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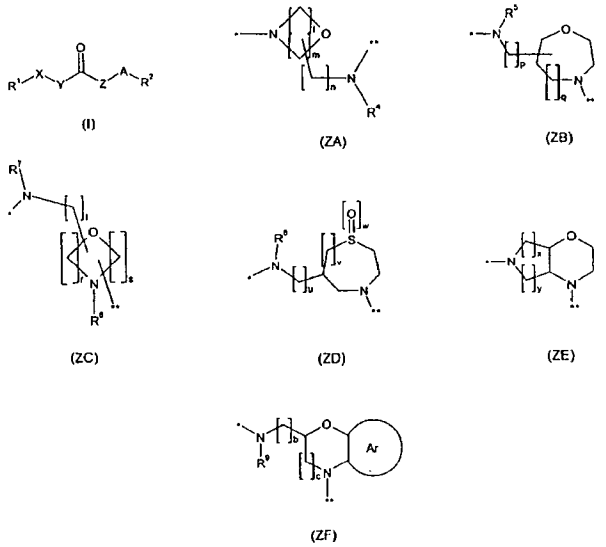
(54) Title: MORPHOLINYLMETHYLUREAS CCR-3 RECEPTOR ANTAGONISTS



(57) Abstract: Compounds of formula (I'): (I); wherein: R^1 represents substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl; X represents $-(CR_{ka}R_{kb})_k-$; R_{ka} and R_{kb} are each independently hydrogen or C_{1-6}alkyl; k is 0-5; Y represents $-NR^3-$ or a bond; R^3 represents hydrogen or C_{1-6}alkyl; Z represents a moiety of formula (ZA), (ZB), (ZC), (ZD), (ZE), or (ZF); A represents $-(CR_{ja}R_{jb})_j-$; R_{ja} and R_{jb} are each independently hydrogen or C_{1-6}alkyl; j is 0, 1 or 2, and; R_2 represents unsubstituted or substituted aryl; and salts and solvates thereof are CCR3 receptor antagonists and are thus indicated to be useful in therapy.

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MORPHOLINYLMETHYLUREAS CCR-3 RECEPTOR ANTAGONISTS

This invention relates to novel compounds, processes for their preparation, pharmaceutical formulations containing them and their use in therapy.

Inflammation is a primary response to tissue injury or microbial invasion and is characterised by leukocyte adhesion to the endothelium, diapedesis and activation within the tissue. Leukocyte activation can result in the generation of toxic oxygen species (such as superoxide anion), and the release of granule products (such as peroxidases and proteases). Circulating leukocytes include neutrophils, eosinophils, basophils, monocytes and lymphocytes. Different forms of inflammation involve different types of infiltrating leukocytes, the particular profile being regulated by the profile of adhesion molecule, cytokine and chemotactic factor expression within the tissue.

The primary function of leukocytes is to defend the host from invading organisms, such as bacteria and parasites. Once a tissue is injured or infected, a series of events occurs which causes the local recruitment of leukocytes from the circulation into the affected tissue. Leukocyte recruitment is controlled to allow for the orderly destruction and phagocytosis of foreign or dead cells, followed by tissue repair and resolution of the inflammatory infiltrate. However in chronic inflammatory states, whereby recruitment is often inappropriate, resolution is not adequately controlled and the inflammatory reaction causes tissue destruction.

There is increasing evidence that the bronchial inflammation which is characteristic of asthma represents a specialised form of cell-mediated immunity, in which cytokine products, such as IL-4 and IL-5 released by T-helper 2 (Th2) lymphocytes, orchestrate the accumulation and activation of granulocytes, in particular eosinophils and to a lesser extent basophils. Through the release of cytotoxic basic proteins, pro-inflammatory mediators and oxygen radicals, eosinophils generate mucosal damage and initiate mechanisms that underlie bronchial hyperreactivity. Therefore, blocking the recruitment and activation of Th2 cells and eosinophils is likely to have anti-inflammatory properties in asthma. In addition, eosinophils have been implicated in other disease types such as rhinitis, eczema, irritable bowel syndrome and parasitic infections.

Chemokines are a large family of small proteins which are involved in trafficking and recruitment of leukocytes (for review see Luster, New Eng. J. Med., 338, 436-445 (1998)). They are released by a wide variety of cells and act to attract and activate various cell types, including eosinophils, basophils, neutrophils, macrophages, T and B lymphocytes. There are two major families of chemokines, CXC- (α) and CC- (β) chemokines, classified according to the

spacing of two conserved cysteine residues near to the amino terminus of the chemokine proteins. Chemokines bind to specific cell surface receptors belonging to the family of G-protein-coupled seven transmembrane-domain proteins (for review see Luster, 1998). Activation of chemokine receptors results in, amongst other responses, an increase in intracellular calcium, changes in cell shape, increased expression of cellular adhesion molecules, degranulation and promotion of cell migration (chemotaxis).

To date a number of CC chemokine receptors have been identified and of particular importance to the current invention is the CC-chemokine receptor-3 (CCR-3), which is predominantly expressed on eosinophils, and also on basophils, mast cells and Th2 cells. Chemokines that act at CCR-3, such as RANTES, MCP-3 and MCP-4, are known to recruit and activate eosinophils. Of particular interest are eotaxin and eotaxin-2, which specifically bind to CCR-3. The localization and function of CCR-3 chemokines indicate that they play a central role in the development of allergic diseases such as asthma. Thus, CCR-3 is specifically expressed on all the major cell types involved in inflammatory allergic responses. Chemokines that act at CCR-3 are generated in response to inflammatory stimuli and act to recruit these cell types to sites of inflammation, where they cause their activation (e.g. Griffiths et al., J. Exp. Med., 179, 881-887 (1994), Lloyd et al., J. Exp. Med., 191, 265-273 (2000)). In addition, anti-CCR-3 monoclonal antibodies completely inhibit eotaxin interaction with eosinophils (Heath, H. *et al.*, J. Clin. Invest. 99 (2), 178-184 (1997)), while an antibody for the CCR-3 specific chemokine, eotaxin, reduced both bronchial hyperreactivity and lung eosinophilia in an animal model of asthma (Gonzalo et al., J. Exp. Med., 188, 157-167 (1998). Thus, many lines of evidence indicate that antagonists at the CCR-3 receptor are very likely to be of therapeutic use for the treatment of a range of inflammatory conditions.

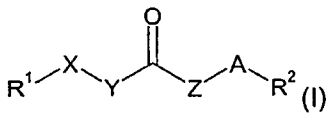
In addition to a key role in inflammatory disorders, chemokines and their receptors also play a role in infectious disease. Mammalian cytomegaloviruses, herpes viruses and pox viruses express chemokine receptor homologues, which can be activated by human CC chemokines such as RANTES and MCP-3 receptors (for review see Wells and Schwartz, Curr. Opin. Biotech., 8, 741-748, 1997). In addition, human chemokine receptors, such as CXCR-4, CCR-5 and CCR-3, can act as co-receptors for the infection of mammalian cells by microbes such as human immunodeficiency viruses (HIV). Thus, chemokine receptor antagonists, including CCR-3 antagonists, may be useful in blocking infection of CCR-3 expressing cells by HIV or in preventing the manipulation of immune cellular responses by viruses such as cytomegaloviruses.

International Patent Application publication number WO 01/24786 (Shionogi & Co. Ltd.) discloses certain aryl and heteroaryl derivatives for treating

diabetes. WO 00/69830 (Torrey Pines Institute for Molecular Studies) discloses certain diazacyclic compounds, and libraries containing them, for biological screening. WO 00/18767 (Neurogen Corporation) discloses certain piperazine derivatives as dopamine D4 receptor antagonists. United States Patent 6,031,097 and WO 99/21848 (Neurogen Corporation) discloses certain aminoisoquinoline derivatives as dopamine receptor ligands. WO 99/06384 (Recordati Industria Chimica) discloses piperazine derivatives useful for the treatment of neuromuscular dysfunction of the lower urinary tract. WO 98/56771 (Schering Aktiengesellschaft) discloses certain piperazine derivatives as anti-inflammatory agents. WO 97/47601 (Yoshitomi Pharmaceutical Industries Ltd.) discloses certain fused heterocyclic compounds as dopamine D-receptor blocking agents. WO 96/39386 (Schering Corporation) discloses certain piperidine derivatives as neurokinin antagonists. WO 96/02534 (Byk Gulden Lomberg Chemische Fabrik GmbH) discloses certain piperazine thiopyridines useful for controlling helicobacter bacteria. WO 95/32196 (Merck Sharp & Dohme Limited) discloses certain piperazine, piperidine, and tetrahydropyridine derivatives as 5-HT1D-alpha antagonists. United States Patent 5,389,635 (E.I. Du Pont de Nemours and Company) discloses certain substituted imidazoles as angiotensin-II antagonists. European Patent Application publication number 0 306 440 (Schering Aktiengesellschaft) discloses certain imidazole derivatives as cardiovascular agents. WO 02/26722 (Glaxo Group Limited) discloses certain morpholine amide derivatives as CCR3 antagonists. WO 02/26723 (Glaxo Group Limited) discloses certain morpholine urea derivatives as CCR3 receptor antagonists.

A novel group of compounds has now been found which are CCR-3 receptor antagonists. These compounds block the migration/chemotaxis of eosinophils and thus possess anti-inflammatory properties. These compounds are therefore of potential therapeutic benefit, especially in providing protection from eosinophil, basophil mast cell and Th2-cell-induced tissue damage in diseases where such cell types are implicated, particularly allergic diseases, including but not limited to bronchial asthma, allergic rhinitis and atopic dermatitis.

Thus, according to one aspect of the invention, there are provided compounds of formula (I):



(I)

wherein:

R^1 represents substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

X represents $-(CR_{ka}R_{kb})_k-$;

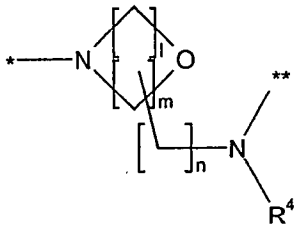
R_{ka} and R_{kb} are each independently hydrogen or C_{1-6}alkyl;

k is 0-5;

Y represents $-NR^3-$ or a bond;

R^3 represents hydrogen or C_{1-6}alkyl;

Z represents a moiety of formula (ZA):



(ZA)

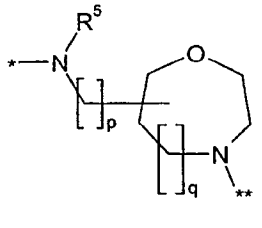
wherein;

l and m are each independently 1 or 2 and l+m is at least 3;

n is 1 or 2, and;

R^4 is hydrogen or C_{1-6}alkyl;

or Z represents a moiety of formula (ZB):



(ZB)

wherein;

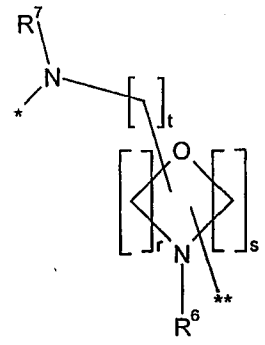
R^5 is hydrogen or C_{1-6}alkyl;

p is 1 or 2, and;

q is 0 or 1;

with the proviso that (ZB) does not represent a 2,4-morphinolyl moiety;

or Z represents a moiety of formula (ZC):



(ZC)

wherein;

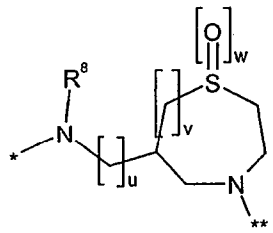
r and s are each independently 1 or 2 and r+s is at least 3;

t is 0, 1, or 2, and;

R^6 is hydrogen or C_{1-6}alkyl;

R^7 is hydrogen or C_{1-6}alkyl;

or Z is a moiety of formula (ZD):



(ZD)

wherein;

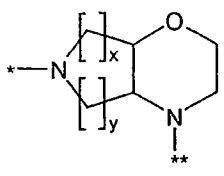
R^8 is hydrogen or C_{1-6}alkyl;

u is 1 or 2;

v is 0 or 1, and;

w is 0, 1, or 2;

or Z is a moiety of formula (ZE)

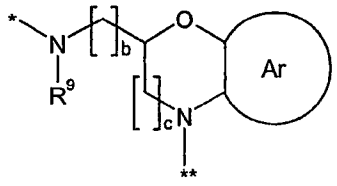


(ZE)

wherein;

x and y are each independently 1 or 2;

or Z represents a moiety of formula (ZF)



(ZF)

wherein;

R^9 is hydrogen or C_{1-6}alkyl;

b is 1 or 2;

c is 1 or 2;

Ar is a 5 or 6-membered aryl group;

A represents $-(CR_{ja}R_{jb})_j-$;

R_{ja} and R_{jb} are each independently hydrogen or C_{1-6}alkyl;

j is 0, 1 or 2, and;

R^2 represents unsubstituted or substituted aryl;

and salts and solvates thereof, with the proviso that the following compounds are excluded;

4-({[({[4-(3,4-dichlorobenzyl)-1,4-oxazepan-2-yl]methyl}amino)carbonyl]--amino}methyl)benzamide.

For the avoidance of doubt, the positions marked '*' and '**' in moieties (ZA), (ZB), (ZC), (ZD), (ZE), and (ZF) indicate the points of attachment of said moieties to the carbonyl group of formula (I) and the -A-R^2 group of formula (I) respectively.

When R^1 is aryl, examples include phenyl.

When R^1 is heteroaryl, examples include tetrazolyl.

When R^1 is substituted aryl, suitable substituents include C_{1-6}alkylsulphonylaminoC_{1-6}alkyl; amino; C_{3-8}cycloalkylaminocarbonyl; C_{1-6}alkylcarbonyl; C_{3-8}cycloalkylcarbonyl; C_{1-6}alkylsulphonylamino; C_{1-6}alkylcarbonylamino; C_{3-8}cycloalkylcarbonylamino; $R^{10}R^{11}NC(O)$-, wherein R^{10} and R^{11} may each independently represent hydrogen or C_{1-6}alkyl, or R^{10} and R^{11} may represent a $-(CH_2)_z-$ group wherein z is 3 to 7 so that, together with the nitrogen atom to which they are attached, a 4 to 8-membered heterocyclyl ring is formed; C_{1-6}alkoxycarbonyl; cyano; aminosulphonyl; aminocarbonyl; halo;

carboxy; C_{1-6}alkyl, hydroxy, nitro; C_{1-6}alkoxy; mono-and di-(C_{1-6}alkyl)amino; or mono- and di-(C_{1-6}alky)laminocarbonyl.

When R^1 is substituted heteroaryl, suitable substituents include C_{1-6}alkylsulphonylaminoC_{1-6}alkyl; amino; C_{3-8}cycloalkylaminocarbonyl; C_{1-6}alkylcarbonyl; C_{3-8}cycloalkylcarbonyl; C_{1-6}alkylsulphonylamino; C_{1-6}alkylcarbonylamino; C_{3-8}cycloalkylcarbonylamino; C_{1-6}alkoxycarbonyl; cyano; aminosulphonyl; aminocarbonyl; halo; carboxy; C_{1-6}alkyl, hydroxy, nitro; C_{1-6}alkoxy; mono-and di-(C_{1-6}alkyl)amino; and mono- and di-(C_{1-6}alky)laminocarbonyl.

Suitably, R^1 is unsubstituted or substituted phenyl.

Suitably, R^1 is substituted tetrazolyl.

When R^1 is substituted phenyl, suitable substituents include C_{3-8}cycloalkylaminocarbonyl, and $R^8R^9NC(O)$- wherein one of R^8 and R^9 is hydrogen and the other is C_{1-6}alkyl.

When R^1 is substituted tetrazolyl, suitable substituents include C_{1-6}alkyl.

Preferably, R^1 is phenyl, 4-(cyclopropylaminocarbonyl)phenyl, 3-(cyclopropylaminocarbonyl)phenyl, 3-aminocarbonylphenyl, 3-(methylaminocarbonyl)phenyl, or 2-methyltetrazol-5-yl.

Suitably, R_{ka} and R_{kb} are both hydrogen.

Suitably, k is 0, 1, or 2.

Suitably, R^3 is hydrogen.

Suitably, l and m are both 2.

Suitably, R^4 is hydrogen or methyl.

Suitably, R^5 is hydrogen.

Suitably, q is 0.

Suitably, r and s are both 2.

Suitably, R^5 is hydrogen or methyl.

Suitably, r is 2.

Suitably, s is 2.

Suitably, t is 1.

Suitably, R^6 is hydrogen or methyl.

Suitably, R^7 is hydrogen.

Suitably, u is 1.

Suitably, v is 0.

Suitably, R^8 is hydrogen.

Suitably, x and y are both 1.

Suitably, b is1.

Suitably, c is 1.

Suitably, R^9 is hydrogen.

Suitably, Ar is unsubstituted benzo.

Suitably, Rja and Rjb are both hydrogen.

Suitably, j is 1.

Examples of the aryl group, R^2, include phenyl.

When R^2 is substituted aryl, suitable substituents include halo, C_{1-6}alkyl, C_{1-6}alkoxycarbonyl, C_{1-6}alkylaminocarbonyl, C_{1-6}alkoxy, nitro, C_{1-6}alkylsulphonyl, hydroxy, C_{1-6}alkoxyC_{1-6}alkyl, C_{1-6}alkylS-, (mono- and-di-C_{1-6}alkyl)amino, and C_{1-6}alkylcarbonylamino.

Suitably, R^2 is substituted phenyl.

When R^2 is substituted phenyl suitable substituents include halo.

More suitably, R^2 is phenyl substituted with chloro.

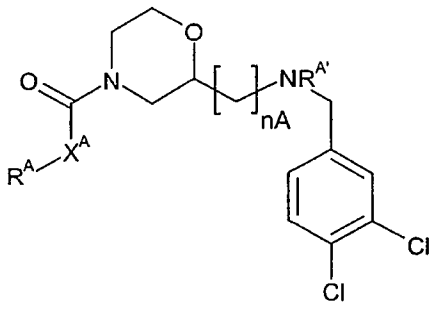
Preferably, R^2 is 3,4-dichlorophenyl.

There exists a subgroup of compounds of formula (I) being of formula (I') wherein the compounds of formula (I') are as hereinbefore defined for formula (I) with the proviso that the following compounds are excluded;

2-methoxy-N-[[4-(phenylmethyl)-3-morpholinyl]methyl]benzamide;
N-(3-cyanophenyl)-N'-[[4-(phenylmethyl)-3-morpholinyl]methyl]urea;
cis-6-benzoyloctahydro-4-(phenylmethyl)pyrrolo[3,4-b]-1,4-oxazine;
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[6-chloro-3,4-dihydro-4- (phenylmethyl)-2H-1,4-benzoxazin-2-yl]methyl]urea;
N-[2-[2-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethyl]phenyl]-N'- [[4-[(4-fluorophenyl)methyl]-3-morpholinyl]methyl]urea;
cis-6-benzoyloctahydro-4-(phenylmethyl)pyrrolo[3,4-b]-1,4-oxazine;
4-amino-5-chloro-2-ethoxy-N-[[4-(phenylmethyl)-3-morpholinyl]methyl]benzamide, and;
4-amino-5-chloro-2-ethoxy-N-[2-[4-(phenylmethyl)-3-morpholinyl]ethyl]benzamide.

There is accordingly provided a compound of formula (I') and salts and solvates thereof.

There exists a preferred subgroup of compounds of formula (I) being of formula (IA)



(IA)

wherein;

R^A is unsubstituted aryl or unsubstituted arylC_{1-6}alkyl;

X^A is a bond or -NH-;

nA is 1 or 2

$R^{A'}$ is C_{1-6}alkyl or hydrogen.

When R^A is aryl, examples include phenyl.

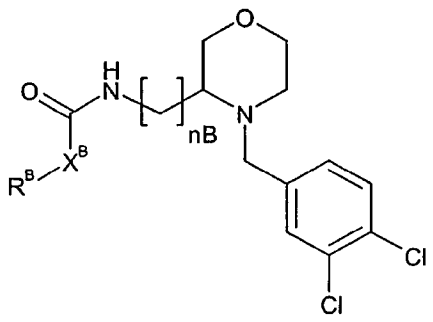
When R^A is arylC_{1-6}alkyl, examples include benzyl and phenylethyl.

Suitably, R is phenyl, benzyl, or phenylethyl.

Suitably, $R^{A'}$ is hydrogen or methyl.

Accordingly, there is provided a compound of formula (IA) or a salt or solvate thereof.

There exists a further preferred subgroup of compounds of formula (I) being of formula (IB)



(IB)

wherein;

R^B is unsubstituted aryl or unsubstituted arylC_{1-6}alkyl;

X^B is -NH- or a bond, and;

nB is 1 or 2.

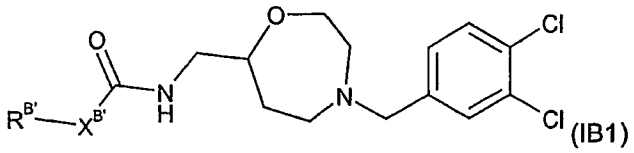
When R^B is aryl, examples include phenyl.

When R^B is arylC_{1-6}alkyl, examples include benzyl and phenylethyl.

Suitably, R^B is phenyl, benzyl, or phenylethyl.

Accordingly, there is provided a compound of formula (IB) or a salt or solvate thereof.

There exists a further preferred subgroup of compounds of formula (I) being of formula (IB1)


(IB1)

wherein;

$R^{B'}$ is unsubstituted aryl or unsubstituted arylC_{1-6}alkyl, and;

$X^{B'}$ is -NH- or a bond.

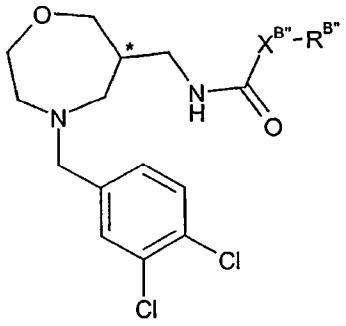
When $R^{B'}$ is aryl, examples include phenyl.

When $R^{B'}$ is arylC_{1-6}alkyl, examples include benzyl and phenylethyl.

Suitably, $R^{B'}$ is phenyl, benzyl, or phenylethyl.

Accordingly, there is provided a compound of formula (IB1) or a salt or solvate thereof.

There exists a further preferred subgroup of compounds of formula (I) being of formula (IB2)


(IB2)

wherein;

$X^{B''}$ is a bond or –NH-, and;

$R^{B''}$ is unsubstituted aryl or unsubstituted arylC_{1-6}alkyl.

When $R^{B''}$ is aryl, examples include phenyl.

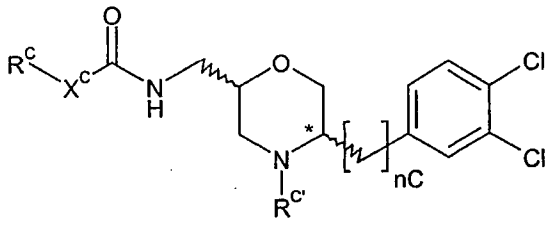
When $R^{B''}$ is arylC_{1-6}alkyl, examples include benzyl and phenylethyl.

Suitably, $R^{B''}$ is phenyl, benzyl, or phenylethyl.

Suitably, the stereochemistry at the position marked '*' is (RS), (R), or (S).

Accordingly, there is provided a compound of formula (IB2) or a salt or solvate thereof.

There exists a further preferred subgroup of compounds of formula (I) being of formula (IC)



(IC)

wherein;

R^C is unsubstituted or aryl or unsubstituted or substituted arylC_{1-6}alkyl;

X^C is –NH- or a bond;

$R^{C'}$ is hydrogen or methyl, and;

nC is 0 or 1.

When R^C is aryl, examples include phenyl.

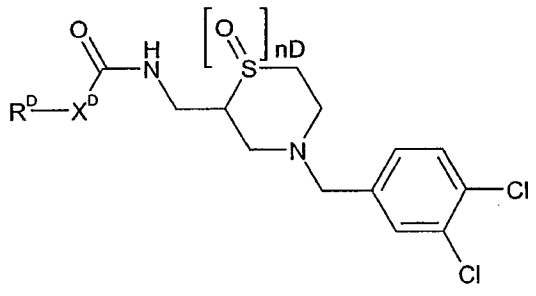
When R^C is arylC_{1-6}alkyl, examples include benzyl and phenylethyl.

Suitably, R^C is phenyl, benzyl, phenylethyl, or 4-(cyclopropylaminocarbonyl)benzyl.

Suitably, the stereochemistry at the position marked '*' is (RS), (R), or (S).

Accordingly, there is provided a compound of formula (IC) or a salt or solvate thereof.

There exists a further preferred subgroup of compounds of formula (I) being of formula (ID)



(ID)

wherein;

R^D is unsubstituted aryl, unsubstituted or substituted arylC_{1-6}alkyl, or substituted heteroaryl;

X^D is a bond or -NH-, and;

nD is 0, 1, or 2.

When R^D is aryl, examples include phenyl.

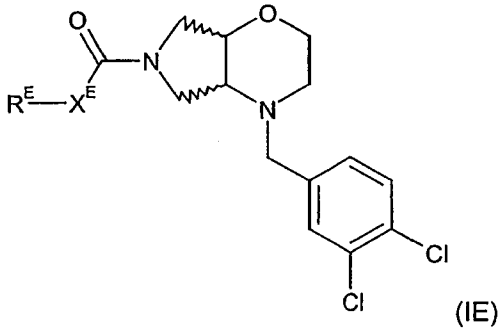
When R^D is arylC_{1-6}alkyl, examples include benzyl and phenylethyl.

When R^D is heteroaryl, examples include tetrazolyl.

Suitably, R^D is benzyl, phenyl, phenylethyl, 4-(cyclopropylaminocarbonyl)benzyl, 3-(cyclopropylaminocarbonyl)benzyl, 3-(aminocarbonyl)benzyl, or 2-methyltetrazol-5-yl.

Accordingly, there is provided a compound of formula (ID) or a salt or solvate thereof.

There exists a further preferred subgroup of compounds of formula (I) being of formula (IE)



(IE)

wherein;

R^E is unsubstituted aryl, or unsubstituted or substituted arylC_{1-6}alkyl, and;

X^E is a bond or -NH-.

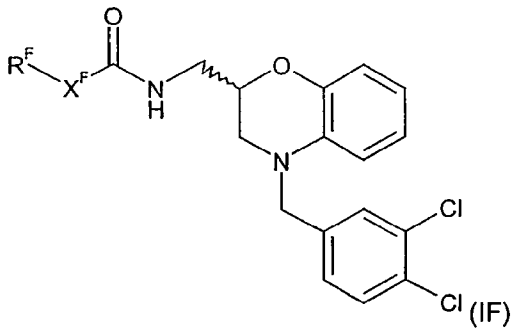
When R^E is aryl, examples include phenyl.

When R^E is arylC_{1-6}alkyl, examples include benzyl and phenylethyl.

Suitably, R^E is benzyl, phenyl, phenylethyl, or 3-(methylaminocarbonyl)benzyl.

Accordingly, there is provided a compound of formula (IE) or a salt or solvate thereof.

There exists a further preferred subgroup of compounds of formula (I) being of formula (IF)



(IF)

wherein;

R^F is unsubstituted or aryl or unsubstituted arylC_{1-6}alkyl, and;

X^F is a bond or -NH-.

When R^F is aryl, examples include phenyl.

When R^F is arylC_{1-6}alkyl, examples include benzyl and phenylethyl.

Suitably, R^F is benzyl, phenyl, or phenylethyl.

Accordingly, there is provided a compound of formula (IF) or a salt or solvate thereof.

Suitable salts of the compounds of formula (I) include physiologically acceptable salts and salts which may not be physiologically acceptable but may be useful in the preparation of compounds of formula (I) and physiologically acceptable salts thereof. If appropriate, acid addition salts may be derived from inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, phosphates, acetates, benzoates, citrates, succinates, lactates, tartrates, fumarates, maleates, 1-hydroxy-2-naphthoates, pamoates, methanesulphonates, formates or trifluoroacetates.

Examples of solvates include hydrates.

Certain of the compounds of formula (I) may contain chiral atoms and/or multiple bonds, and hence may exist in one or more stereoisomeric forms. The present invention encompasses all of the stereoisomers of the compounds of formula (I), including geometric isomers and optical isomers, whether as individual stereoisomers or as mixtures thereof including racemic modifications.

Generally it is preferred that a compound of formula (I) is in the form of a single enantiomer or diastereoisomer.

Certain of the compounds of formula (I) may exist in one of several tautomeric forms. It will be understood that the present invention encompasses all of the tautomers of the compounds of formula (I) whether as individual tautomers or as mixtures thereof.

References to 'aryl' refers to monocyclic and bicyclic carbocyclic aromatic rings, for example naphthyl and phenyl, especially phenyl. When an aryl group is part of a fused ring system, then 'aryl' refers to a monocyclic carbocyclic aromatic residue, for example benzo.

Suitable substituents for any aryl group include 1 to 5, suitably 1 to 3, substituents selected from the list consisting of cyano, perhaloalkyl, amido, halo, alkyl, alkoxycarbonyl, aminocarbonyl, mono- and di-(alkyl)aminocarbonyl, alkoxy, nitro, alkylsulphonyl, hydroxy, alkoxyalkyl, alkylthio, mono- and-di-(alkyl)amino, and alkylcarbonylamino.

References to 'heteroaryl' refers to monocyclic heterocyclic aromatic rings containing 1-4 heteroatoms selected from nitrogen, oxygen and sulphur. Examples of heterocyclic aromatic rings include tetrazolyl.

Suitable substituents for any heteroaryl group include 1 to 5, suitably 1 to 3, substituents selected from the list consisting of aminocarbonyl; mono-and di-(alkyl)aminocarbonyl; cycloalkylaminocarbonyl; amino; alkylsulphonylamino; alkylcarbonyl; alkyl; alkoxycarbonyl; unsubstituted heteroaryl; heteroaryl substituted with alkyl, halo, alkoxy, or hydroxy; halo; alkoxy; nitro; alkylsulphonyl; hydroxy; alkoxyalkyl; alkylthio; mono- and-di-(alkyl)amino; alkylcarbonylamino; cyano, perhaloalkyl; amido; and alkylthio.

References to 'alkyl' include references to both straight chain and branched chain aliphatic isomers of the corresponding alkyl, suitably containing up to six carbon atoms.

References to 'cycloalkyl' include saturated alicyclic rings suitably containing 3-8 carbon atoms.

Suitable substituents for any cycloalkyl group include alkyl, halo, and hydroxy.

References to 'heterocyclyl' refer to monocyclic heterocyclic aliphatic rings containing 2 to 6, suitably 3 to 5, carbon atoms, and 1 to 3, heteroatoms selected from nitrogen, oxygen, and sulphur. Examples of heterocyclic rings include piperidinyl.

Suitable substituents for any heterocyclyl group include cycloalkylcarbonyl, aminocarbonyl, alkylsulphonylamino, alkylcarbonyl, cycloalkylaminocarbonyl, alkyl, alkoxycarbonyl, alkylaminocarbonyl, halo, alkoxy, nitro, alkylsulphonyl, hydroxy, alkoxyalkyl, alkylthio, mono- and di-(alkyl)amino, and alkylcarbonylamino.

References to 'halogen' or 'halo' include iodo, bromo, chloro or fluoro, especially fluoro and chloro.

The compounds of formula (I) and salts and solvates thereof may be prepared by the methodology described hereinafter, constituting further aspects of this invention.

Accordingly, there are provided processes for the preparation of a compound of formula (I) wherein Y represents $-NR^3-$ which processes are denoted Synthetic Method A and Synthetic Method C.

Synthetic Method A may be performed as either of two alternatives; Alternative (i) and Alternative (ii).

Alternative (i): the reaction of a compound of formula (II), or a protected form thereof, with a compound of formula (III);

$$R^1\text{-}X\text{-}N(R^3)U_g \text{ (II)} \qquad R^2\text{-}A\text{-}ZH \text{ (III)}$$

or;

Alternative (ii): the reaction between a compound of formula (V), or a protected form thereof, with a compound of formula (IV);

R^2-A-Z-U_g (V) R^1-X-N(R^3)H (IV)

wherein;

R^1, X, R^3, R^2, A, and Z are as hereinbefore defined, and U_g is a urea-forming group,

and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing a salt or solvate of the compound so formed.

A urea-forming group is a group which is derived from a reagent which introduces a carbonyl group and a leaving group to an amino compound. Examples of urea-forming groups are imidazolylcarbonyl and chlorocarbonyl, and, when R^3 is hydrogen, 4-nitrophenoxycarbonyl may be used. The reagents from which they are derived are 1,1'-carbonyldiimidazole, phosgene, and 4-nitrophenylchloroformate respectively.

For Alternative (i), a compound of formula (II) may be prepared by the reaction of a compound of formula (IV)

R^1-X-N(R^3)H (IV)

with a compound of formula U_g-L_g wherein R^1, X, R^3, and U_g are as hereinbefore defined, and L_g is a leaving group. A suitable leaving group, L_g, is a halo group such as chloro, or an imidazolyl group.

Typically, a compound of formula (IV) is reacted with a compound of formula U_g-L_g followed by reaction with a compound of formula (III) *in situ* i.e. without isolation of a compound of formula (II).

For example, a solution of a compound of formula (IV) and a suitable base, such as diisopropylethylamine, in a suitable solvent, such as acetonitrile is added dropwise to a stirred solution of a compound of formula U_g-L_g in the suitable solvent. The solution is stirred for a suitable period of time, such as 1.5-2 hours, then treated with a solution of a compound of formula (III) in the suitable solvent. The reaction mixture is stirred for a suitable period of time, for example 4-6 hours, then left to stand for up to 18 hours. The solvent is removed *in vacuo* and the crude compound of formula (I) isolated by conventional means. Purification may be undertaken by conventional means such as chromatography.

For Alternative (ii), typically a compound of formula (IV) in a suitable anhydrous solvent, such as anhydrous acetonitrile, is treated with a compound of formula (V) and a suitable base such as diisopropylethylamine. The mixture is stirred for 16-20 hours and purified by chromatography to give a compound of formula (I).

A compound of formula (V) may be prepared by reaction of a compound of formula (III) as hereinbefore defined with a compound of formula U_g-L_g as hereinbefore defined.

Typically, a solution of compound of formula U_g-L_g in a suitable anhydrous solvent, such as anhydrous dichloromethane, at a suitable reduced temperature, such as minus 5 to 5°C, is treated, dropwise, with a solution of a compound of formula (III) and a suitable base, such as triethylamine, in the suitable anhydrous solvent. After stirring at ambient temperature for up to 20 hours the mixture is concentrated *in vacuo* and the residue purified by chromatography to yield a compound of formula (V).

Synthetic Method C comprises the reaction of a compound of formula (III) as hereinbefore defined, or a protected form thereof, with a compound of formula (VI);

$$R^1\text{-}X\text{-}NCO \quad (VI)$$

wherein R^1 and X are as hereinbefore defined, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing a salt or solvate of the compound so formed.

Typically, a solution of a compound of formula (III) in a suitable anhydrous solvent, such as dichloromethane, is treated with a suitable base, such as triethylamine, and a compound of formula (VI) and stirred at ambient temperature for 12-20 hours. The compound of formula (I) is then isolated typically by chromatography.

In a still further aspect, there is provided a process for the preparation of a compound of formula (I) wherein Y is a bond which process is denoted Synthetic Method B.

Synthetic Method B comprises the reaction of a compound of formula (VII)

$$R^1\text{-}X\text{-}COOH \quad (VII)$$

wherein R^1 and X are as hereinbefore defined, with a compound of formula (III) as hereinbefore defined in the presence of a suitable activating agent, such as O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU).

Typically, a solution of a compound of formula (VII) and a suitable activating agent, such as HATU, in a suitable solvent such as acetonitrile is stirred for a few minutes then treated with a solution of a compound of formula (III) and a suitable base, such as diisopropylethylamine, in the suitable solvent. The reaction mixture is stirred for 1-3 hours then left to stand for 12-18 hours. The solvent is removed *in vacuo*. The crude product is then isolated and purified using conventional techniques.

Compounds of formulae (III), (IV), (VI), and (VII) are known, commercially available compounds and/or may be prepared by analogy with procedures disclosed in standard reference texts of synthetic methodology such as *J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience,* by analogy with procedures disclosed herein, or by analogy with procedures disclosed in WO 02/26723 and WO 02/26722.

It is considered that compounds of formula (III) are novel. Accordingly there is also provided a compound of formula (III) or a salt or solvate thereof.

The above mentioned conversion of a compound of formula (I) into another compound of formula (I) includes any conversion which may be effected using conventional procedures, for example those disclosed in standard reference texts of synthetic methodology such as *J. March, Advanced Organic Chemistry, 3rd Edition (1985), Wiley Interscience.*

As previously mentioned herein, the processes of the invention may optionally include the removal of any necessary protecting group. Examples of the use of protection and deprotection steps disclosed herein include the use of *tert*-butoxycarbonyl (t-BOC) and trifluoroacetyl (TFA) protecting groups for amines. Specifically, the use of t-BOC protection/deprotection in Synthetic Methods B and C are denoted herein as Synthetic Methods D and F respectively, while the use of TFA protection/deprotection in Synthetic Methods B and C are denoted herein as Synthetic Methods E and G respectively.

Suitable protecting groups in any of the above mentioned reactions are those used conventionally in the art. The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected, for example those methods discussed in standard reference texts of synthetic methodology such as *P J Kocienski, Protecting Groups, (1994), Thieme.*

Where appropriate individual stereoisomeric forms of the compounds of formula (I) may be prepared as individual isomers using conventional procedures

such as the fractional crystallisation of diastereoisomeric derivatives or chiral high performance liquid chromatography (chiral HPLC).

The absolute stereochemistry of compounds may be determined using conventional methods, such as X-ray crystallography.

The salts and solvates of the compounds of formula (I) or formula (III) may be prepared and isolated according to conventional procedures.

Compounds of the invention may be tested for *in vitro* biological activity in accordance with the following assay:

CCR-3 Binding Assay

A CCR-3 competition binding SPA (scintillation proximity assay) was used to assess the affinity of novel compounds for CCR-3. Membranes prepared from K562 cells stably expressing CCR-3 (2.5μg/well) were mixed with 0.25mg/well wheat-germ agglutinin SPA beads (Amersham) and incubated in binding buffer (HEPES 50 mM, $CaCl_2$ 1 mM, $MgCl_2$ 5 mM, 0.5% BSA) at 4°C for 1.5 hr. Following incubation, 20 pM of [^{125}I] eotaxin (Amersham) and increasing concentrations of compound (1pM to 30μM) were added and incubated in a 96 well plate for 2 hr at 22°C then counted on a Microbeta plate counter. The total assay volume was 100 μl. Competition binding data were analysed by fitting the data with a four parameter logistic equation. Data are presented as the mean pIC_{50} values (negative logarithm of the concentration of compound which inhibits [^{125}I]eotaxin binding by 50%) from at least two experiments.

The compounds of the Examples tested in the CCR-3 binding assay and possessed pIC50 values in the range 4 to 7

Examples of disease states in which the compound of the invention has potentially beneficial anti-inflammatory effects include diseases of the respiratory tract such as bronchitis (including chronic bronchitis), bronchiectasis, asthma (including allergen-induced asthmatic reactions), chronic obstructive pulmonary disease (COPD), cystic fibrosis, sinusitis and rhinitis. Other relevant disease states include diseases of the gastrointestinal tract such as intestinal inflammatory diseases including inflammatory bowel disease (e.g. Crohn's disease or ulcerative colitis) and intestinal inflammatory diseases secondary to radiation exposure or allergen exposure.

Furthermore, the compound of the invention may be used to treat nephritis, skin diseases such as psoriasis, eczema, allergic dermatitis and hypersensitivity reactions and diseases of the central nervous system which have an inflammatory component (e.g. Alzheimer's disease, meningitis, multiple sclerosis) HIV and AIDS dementia.

Compounds of the present invention may also be of use in the treatment of nasal polyposis, conjunctivitis or pruritis.

Further examples of disease states in which the compound of the invention have potentially beneficial effects include cardiovascular conditions such as atherosclerosis, peripheral vascular disease and idiopathic hypereosinophilic syndrome. Other diseases for which the compound of the present invention may be beneficial are other hypereosinophilic diseases such as Churg-strauss syndrome. Additionally, eosinophilia is commonly found in parasitic diseases, especially helminth infections, and thus the compound of the present invention may be useful in treating inflammation arising from hyper-eosinophilic states of diseases such as hydatid cyst (Echinococcus sp.), tapeworm infections (Taenia sp.), blood flukes (schistosomiasis), and nematode (round worms) infections such as:- Hookworm (Ancylostoma sp.), Ascaris, Strongyloides, Trichinella, and particularly lymphatic filariasis including Onchocerca, Brugia, Wucheria (Elephantiasis).

The compound of the invention may be useful as an immunosuppressive agent and so have use in the treatment of auto-immune diseases such as allograft tissue rejection after transplantation, rheumatoid arthritis and diabetes. Compounds of the invention may also be useful in inhibiting metastasis.

Diseases of principal interest include asthma, COPD and inflammatory diseases of the upper respiratory tract involving seasonal and perennial rhinitis.

Preferred diseases of principal interest include asthma and inflammatory diseases of the upper respiratory tract involving seasonal and perennial rhinitis. Further diseases also of principle interest include inflammatory diseases of the gastrointestinal tract such as inflammatory bowel disease.

It will be appreciated by those skilled in the art that references herein to treatment or therapy extend to prophylaxis as well as the treatment of established conditions.

As mentioned above, compounds of formula (I) are useful as therapeutic agents.

There is thus provided as a further aspect of the invention a compound of formula (I') or a physiologically acceptable salt or solvate thereof for use as an active therapeutic agent.

There is also therefore provided a compound of formula (I'), or a physiologically acceptable salt or solvate thereof, for use in the treatment of inflammatory conditions, eg. asthma or rhinitis.

According to another aspect of the invention, there is provided the use of a compound of formula (I) or a physiologically acceptable salt or solvate thereof for the manufacture of a medicament for the treatment of patients with inflammatory conditions, eg. asthma or rhinitis.

In a further or alternative aspect there is provided a method for the treatment of a human or animal subject with an inflammatory condition eg.

asthma or rhinitis, which method comprises administering an effective amount of a compound of formula (I) or a physiologically acceptable salt or solvate thereof.

The compounds according to the invention may be formulated for administration in any convenient way.

There is thus further provided a pharmaceutical composition comprising a compound of formula (I'), or a physiologically acceptable salt or solvate thereof, and optionally one or more physiologically acceptable diluents or carriers.

There is also provided a process for preparing such a pharmaceutical formulation which comprises admixing the compound of formula (I') or a physiologically acceptable salt or solvate thereof with one or more physiologically acceptable diluents or carriers.

The compounds according to the invention may, for example, be formulated for oral, inhaled, intranasal, buccal, parenteral or rectal administration, preferably for oral administration.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch, cellulose or polyvinyl pyrrolidone; fillers, for example, lactose, microcrystalline cellulose, sugar, maize- starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch, croscarmellose sodium or sodium starch glycollate; or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art.

Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxymethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; or preservatives, for example, methyl or propyl p- hydroxybenzoates or sorbic acid. The preparations may also contain buffer salts, flavouring, colouring and/or sweetening agents (e.g. mannitol) as appropriate.

For buccal administration the compositions may take the form of tablets or lozenges formulated in conventional manner.

The compounds may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

The compounds according to the invention may also be formulated for parenteral administration by bolus injection or continuous infusion and may be presented in unit dose form, for instance as ampoules, vials, small volume infusions or pre-filled syringes, or in multidose containers with an added preservative. The compositions may take such forms as solutions, suspensions, or emulsions in aqueous or non-aqueous vehicles, and may contain formulatory agents such as anti-oxidants, buffers, antimicrobial agents and/or tonicity adjusting agents. Alternatively, the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use. The dry solid presentation may be prepared by filling a sterile powder aseptically into individual sterile containers or by filling a sterile solution aseptically into each container and freeze-drying.

The compounds and pharmaceutical compositions according to the invention may also be used in combination with other therapeutic agents, for example antihistaminic agents, anticholinergic agents, anti-inflammatory agents such as corticosteroids, e.g. fluticasone propionate, beclomethasone dipropionate, mometasone furoate, triamcinolone acetonide or budesonide; or non-steroidal anti-inflammatory drugs (NSAIDs) eg. sodium cromoglycate, nedocromil sodium, PDE-4 inhibitors, leukotriene antagonists, iNOS inhibitors, tryptase and elastase inhibitors, beta-2 integrin antagonists and adenosine 2a agonists; or beta adrenergic agents such as salmeterol, salbutamol, formoterol, fenoterol or terbutaline and salts thereof; or antiinfective agents e.g. antibiotic agents and antiviral agents. It will be appreciated that when the compounds of the present invention are administered in combination with other therapeutic agents normally administered by the inhaled or intranasal route, that the resultant pharmaceutical composition may be administered by the inhaled or intranasal route.

Compounds of the invention may conveniently be administered in amounts of, for example, 0.001 to 500mg/kg body weight, preferably 0.01 to 500mg/kg body weight, more preferably 0.01 to 100mg/kg body weight, and at any appropriate frequency e.g. 1 to 4 times daily. The precise dosing regimen will of course depend on factors such as the therapeutic indication, the age and condition of the patient, and the particular route of administration chosen.

Throughout the description and the claims which follow, unless the context requires otherwise, the word 'comprise', and variations such as 'comprises' and 'comprising', will be understood to imply the inclusion of a stated integer or step or group of integers but not to the exclusion of any other integer or step or group of integers or steps.

The invention is illustrated by reference to, but is in no way limited by, the following Examples.

It should be noted that, for clarity, compounds of the Intermediates and the Examples are referred to by number, for example "Intermediate 3" and "Example 26". The structures of the compounds so referred to are given in Tables A to F inclusive for the Examples and Tables G to V inclusive for the Intermediates.

General Experimental Details

Standard Automated Preparative HPLC column, conditions and eluent

Automated preparative high performance liquid chromatography (autoprep. HPLC) was carried out using a Supelco+ 5μm (100mm x 22mm internal diameter) column eluted with a mixture of solvents consisting of (i) 0.1% trifluoroacetic acid in water and (ii) 0.1% trifluoroacetic acid in acetonitrile, the eluent being expressed as the percentage of (ii) in the solvent mixture, at a flow rate of 4ml per minute.

Standard chiral analytical HPLC system

This system used a 250 x 4.6mm Chiralpak AD 10μm column, eluting with absolute ethanol:heptane mixtures at a flow rate of 1ml per minute, with UV detection at 215nm.

Standard chiral preparative HPLC system

This system used a Chiralpak AD column (2cm x 25cm), eluting with absolute ethanol:heptane mixtures (15ml/min over 25mins, UV detection at 215nm).

Intermediate 1

A solution of 2-ethoxycarbonyl-2-dehydro-1,4-thiazine [CAS101417-21-4] (4.0g) in anhydrous tetrahydrofuran (50ml) was added to a stirred suspension of sodium hydride 60% dispersion in oil (1.02g) and allowed to stir for 1 hour when 3,4-dichlorobenzyl bromide (5.55g) was added. After stirring at room temperature for 4 hours the mixture was concentrated *in vacuo*. The residue was partitioned between ethyl acetate /water, washed with 10% sodium bicarbonate solution and ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 50g), eluting with a gradient of ethyl acetate/cyclohexane, gave the title compound (7.0g) from ethyl acetate as a yellow oil.
LC-MS (System A): Rt = 3.56 min. Mass Spectrum *m/z* 332[MH+]

Intermediate 2

A solution of Intermediate 1 (0.5g) in anhydrous tetrahydrofuran (5ml) was added to lithium aluminium hydride 1M solution in tetrahydrofuran (3ml) and stirred at room temperature overnight. The mixture was quenched by careful addition of ethyl acetate (20ml) and water (1ml). After vigorous stirring for 10min the mixture was filtered and concentrated *in vacuo*. Chromatographic separation on silica

(Varian Bond-Elut™, 5g), eluting with a gradient of ethyl acetate/cyclohexane gave the title compound (0.18g) from ethyl acetate as a colourless oil.
LC-MS (System A): Rt = 2.11min. Mass Spectrum *m/z* 292[MH+]

Intermediate 3
A solution of Intermediate 2 (2.0g) in anhydrous chloroform (60ml) was treated with thionyl chloride (1.565g) and heated to reflux for 20mins. The mixture was cooled and concentrated *in vacuo* then partitioned between chloroform/10% sodium bicarbonate dried ($MgSO_4$) and concentrated *in vacuo*. The crude title compound (2.1g) was used in the next stage of synthesis without purification.
LC-MS (System A): Rt = 3.56 min. Mass Spectrum *m/z* 331[MH+]

Intermediate 4
A solution of Intermediate 3 (2.1g) in anhydrous acetonitrile (100ml0 was treated with sodium azide (0.53g) and heated to reflux for 2 hours then concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 20g), eluting with a gradient of ethyl acetate/cyclohexane gave the title compound (1.04g) from 1:9 ethyl acetate/cyclohexane as a pale yellow oil.
LC-MS (System A): Rt = 3.90min. Mass Spectrum *m/z* 318[MH+]

Intermediate 5
A solution of Intermediate 4 (0.95g) in anhydrous toluene (10ml) at 0°C was treated, dropwise, with sodium bis(2-methoxyethoxy)aluminium hydride 65+ wt. % in toluene (1.8ml) and warmed to room temperature for 1 hour. The mixture was quenched at 0°C by cautious addition of water followed by 48% sodium hydroxide, separated and dried ($MgSO_4$). Concentrated *in vacuo* to give the title compound (0.84g) as a pale yellow oil.
LC-MS (System A): Rt = 1.95min. Mass Spectrum *m/z* 292[MH+]

Intermediate 6
A solution of Intermediate 5 (0.42g) in anhydrous dichloromethane (10ml) was treated with di-tert-butyldicarbonate (0.315g) and triethylamine (0.2ml). The mixture was stirred at room temperature for 18hrs and chromatographic purification on silica (Varian Bond-Elut™, 10g), eluting with 1:4 ethyl acetate/cyclohexane gave the title compound (0.56g) as a colourless oil.
LC-MS (System A): Rt = 2.97min. Mass Spectrum *m/z* 335[MH+ -57 (Bu^t]

Intermediate 7
A solution of Intermediate 6 (0.05g) in methanol (10ml) at 0°C was added, dropwise, a saturated solution of sodium periodate (0.027g) in water over 5min.

The mixture was stirred at 0-5°C for 1hr. Concentrated *in vacuo* and partitioned between dichloromethane/10% sodium bicarbonate solution dried ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 2g), eluting with a gradient of ethyl acetate/cyclohexane gave the title compound (0.045g) from ethyl acetate as a colourless gum.
LC-MS (System A): Rt = 2.96 and 3.14min. Mass Spectrum *m/z* 407[MH+]

Intermediate 8

A solution of Intermediate 7 (0.04g) in dichloromethane (1ml) was treated with trifluoroacetic acid (1ml) and allowed to stand for 1hr at room temperature. Concentration *in vacuo* gave the title compound (0.4g) as a colourless gum.
LC-MS (System A): Rt = 2.17 and 2.25min. Mass Spectrum *m/z* 307[MH+]

Intermediate 9

A solution of Intermediate 6 (0.05g) in acetonitrile (3ml) was treated dropwise, over 1min, with a solution of sodium periodate (0.057g) in water (2.8ml). To this was added ruthenium chloride (1mg) and the mixture stirred for 2hrs partitioned between ethyl acetate (10ml) and 10% sodium bicarbonate (10ml), dried ($MgSO_4$). Concentration *in vacuo* gave the title compound (0.05g) as a pale yellow gum.
LC-MS (System A): Rt = 3.49min. Mass Spectrum *m/z* 423[MH+]

Intermediate 10

A solution of Intermediate 7 (0.025g) in dichloromethane (1ml) was treated with trifluoroacetic acid (1ml) and allowed to stand for 1hr at room temperature. Concentration *in vacuo* gave the title compound (0.032g) as a colourless gum.
LC-MS (System A): Rt = 2.01min Mass Spectrum *m/z* 339[MH+]

Intermediate 11

A melt of (-)-2-amino-3-(3,4-dichlorophenyl)propanol [CAS 37844-08-9] (7.7g) at 80°C was treated with 2,3-epoxypropylphthalimide [CAS5455-98-1] (8.54g) and stirred for 3.5hrs. The mixture was treated with concentrated sulphuric acid (11.9ml) and heated to 150°C for 18hrs, cooled and made alkaline using 2 M sodium hydroxide then extracted three times with ethyl acetate . The mixture was filtered through celite then washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification on silica (flash column) using 10% methanol/chloroform/1% 880 ammonia solution gave the title compound (2.2g) as a dark brown gum.
LC-MS (System A): Rt = 1.76min. Mass Spectrum *m/z* 275[MH^+]

Intermediate 12

A solution of Intermediate 11 (1.84g) in methanol(70ml) was treated with ethyl trifluoroacetate(0.8ml) and triethylamine(0.93ml) at room temp for 3hrs. The mixture was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 50g), eluting with a gradient of cyclohexane /ethyl acetate/methanol gave the title compound (1.30g) as a diastereomeric mixture from 19:1ethyl acetate/methanol as a colourless gum

LC-MS (System A): Rt = 2.48 & 2.54min. Mass Spectrum *m/z* 371[MH+].

Intermediate 13

A solution of Intermediate 12 (0.20g) in anhydrous dichloromethane(5ml) was treated with di-tert-butyl dicarbonate(0.14g) and triethylamine(0.19ml) at room temp for 18hrs. The mixture was washed with water(10ml) and the organic phase was separated through a hydrophobic frit and concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 20g), eluting with a gradient of cyclohexane /ethyl acetate gave the title compound (0.20g) from 1:1cyclohexane/ethyl acetate as a brown foam.

LC-MS (System A): Rt = 3.70min. Mass Spectrum *m/z* 488[MH+]+ NH_4^+.

Intermediate 14

A solution of Intermediate 13 (0.19g) in ethanol (10ml) was treated with a 5% aqueous solution of potassium carbonate (10ml) at room temp for 3days. The mixture was concentrated *in vacuo* and partitioned between water (20ml) and dichloromethane (20ml). The aqueous phase was extracted with dichloromethane(20ml) and the combined organic phases was washed with brine(30ml). The organic phase was separated through a hydrophobic frit and concentrated *in vacuo* to give the title compound (0.15g) as a brown gum.

LC-MS (System A): Rt = 2.70min. Mass Spectrum *m/z* 375[MH+]

Intermediate 15A

Intermediate 15A was prepared by Synthetic Method B using Intermediate 14 (0.03g), in dry dimethylformamide(3ml), benzoic acid(0.01g), HATU(0.03g) and diisopropylethylamine(0.017ml). The title compound (0.03g) was obtained from 1:1 cyclohexane/ethyl acetate as a colourless gum.

LC-MS (System A): Rt = 3.67min. Mass Spectrum *m/z* 479[MH+].

Intermediate 15B

Intermediate 15B was prepared by Synthetic Method B using Intermediate 14 (0.03g), in dry dimethylformamide(3ml), phenylacetic acid(0.01g), HATU(0.03g)

and diisopropylethylamine(0.017ml). The title compound (0.02g) was obtained from 1:1 cyclohexane/ethyl acetate as a colourless gum.
LC-MS (System A): Rt = 3.66min. Mass Spectrum *m/z* 493[MH+].

Intermediate 15C
Intermediate 15C was prepared by Synthetic Method B using Intermediate 14 (0.03g), in dry dimethylformamide(3ml), phenylpropionic acid(0.01g), HATU(0.03g) and diisopropylethylamine(0.017ml). The title compound (0.02g) was obtained from 1:1 cyclohexane/ethyl acetate as a colourless gum.
LC-MS (System A): Rt = 3.73min. Mass Spectrum *m/z* 507[MH+].

Intermediate 16A
Intermediate 16A was prepared by Synthetic Method C using Intermediate 14 (0.03g), in dry acetonitrile(2ml), benzyl isocyanate(0.01ml), and triethylamine(0.028ml). The title compound (0.02g) was obtained from ethyl acetate as a colourless gum.
LC-MS (System A): Rt = 3.64min. Mass Spectrum *m/z* 508[MH+].

Intermediate 16B
Intermediate 16B was prepared by Synthetic Method C using Intermediate 14 (0.03g), in dry acetonitrile(2ml), phenethyl isocyanate(0.01ml), and triethylamine(0.028ml). The title compound (0.02g) was obtained from ethyl acetate as a colourless gum.
LC-MS (System A): Rt = 3.69min. Mass Spectrum *m/z* 522[MH+].

Intermediate 17
A solution of Intermediate 12 (0.57g) in ethanol (15ml) was treated with methyl iodide(0.15ml) and potassium carbonate(0.42g) at room temp for 2days. The solid was filtered off and the filtrate concentrated *in vacuo*. The residue was partitioned between dichloromethane(50ml) and water(50ml). The organic phase was separated through a hydrophobic frit and concentrated *in vacuo*. Chromatographic purification by SCX (IST Isolute ™, 10g), eluting with methanol and 10% ammonia solution/methanol to give the title compound (0.1g) as a brown oil.
LC-MS (System A): Rt = 2.57min. Mass Spectrum *m/z* 385[MH+].

Intermediate 18
Intermediate 18 was prepared in a similar manner to Intermediate 14 using Intermediate 17 (0.1g) in ethanol(10ml) and potassium carbonate solution(2ml) to give the title compound (0.080g) as a brown gum.

LC-MS (System A): Rt = 1.84min. Mass Spectrum *m/z* 289[MH+].

Intermediate 19

A melt of (+)-2-amino-3-(3,4-dichlorophenyl)propanol [CAS 37844-09-0] (1.1g) at 80°C was treated with 2,3-epoxypropylphthalimide [CAS5455-98-1] (1.22g) and stirred for 3.5hrs. The mixture was treated with concentrated sulphuric acid (1.7ml) and heated to 150°C for 18hrs, cooled and made alkaline using 2 M sodium hydroxide then extracted three times with ethyl acetate . The mixture was filtered through Celite then washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification on silica (flash column) using 10% methanol/chloroform/1% 880 ammonia solution gave the title compound (0.125g) as a dark brown gum.

LC-MS (System A): Rt = 0.91min. Mass Spectrum *m/z* 275[MH^+]

Intermediate 20

Intermediate 20 was prepared in a similar manner to Intermediate 12 using Intermediate 19 (2g) in methanol (60ml), triethylamine (1ml) and ethyl trifluoroacetate (0.86ml) to give the title compound (1.14g) as a diastereomeric mixture from ethyl acetate as an orange oil.

LC-MS (System A): Rt = 2.43 and 2.5min. Mass Spectrum *m/z* 371[MH+]

Intermediate 21

Intermediate 21 was prepared in a similar manner to Intermediate 13 using Intermediate 20 (0.32g) in dichloromethane (20ml) and Di-t-butyl dicarbonate (0.19g) to give the title compound (0.4g) as a diastereomeric mixture form 1:1 ethyl acetate/cyclohexane as a yellow oil.

LC-MS (System A): Rt = 3.71min. Mass Spectrum *m/z* 469[MH-]

Intermediate 22

Intermediate 22 was prepared in a similar manner to Intermediate 14 using Intermediate 22 (0.4g) in ethanol (10ml) and 5% aqueous potassium carbonate solution (10ml) to give the title compound (0.28g) as a diastereomeric mixture as a yellow oil.

LC-MS (System A): Rt = 2.65 and 2.68min. Mass Spectrum *m/z* 375[MH+]

Intermediate 23A

Intermediate 23A was prepared by Synthetic Method B using Intermediate 22 (0.06g) in dry dimethylformamide (3ml), benzoic acid (0.0195g), HATU (0.061g) and diisopropylethylamine (0.028ml). The title compound (0.069g) was obtained as a diastereomeric mixture as a colourless oil.

LC-MS (System A): Rt = 3.63min. Mass Spectrum *m/z* 479[MH+]

Intermediate 23B

Intermediate 23B was prepared by Synthetic Method B using Intermediate 22 (0.06g) in dry dimethylformamide (3ml), phenylacetic acid (0.022g), HATU (0.061g) and diisopropylethylamine (0.028ml). The title compound (0.074g) was obtained as a diastereomeric mixture as a colourless oil.
LC-MS (System A): Rt = 3.62min. Mass Spectrum *m/z* 493[MH+]

Intermediate 23C

Intermediate 23C was prepared by Synthetic Method B using Intermediate 22 (0.06g) in dry dimethylformamide (3ml), hydrocinnamic acid (0.024g), HATU (0.061g) and diisopropylethylamine (0.028ml). The title compound (0.068g) was obtained as a diastereomeric mixture as a colourless oil.
LC-MS (System A): Rt = 3.69 and 3.73min. Mass Spectrum *m/z* 507[MH+]

Intermediate 23D

Intermediate 23D was prepared by Synthetic Method B using Intermediate 22 (0.053g) in dry dimethylformamide (4ml), Intermediate 83 (0.031g), HATU (0.054g) and diisopropylethylamine (0.024ml). The title compound (0.035g) was obtained as a diastereomeric mixture as a colourless oil.
LC-MS (System A): Rt = 3.4min. Mass Spectrum *m/z* 576[MH+]

Intermediate 24A

Intermediate 24A was prepared by Synthetic Method C using Intermediate 22 (0.045g) in dry acetonitrile (2ml), benzyl isocyanate (0.018ml) and triethylamine (0.042ml). The title compound (0.061g) was obtained as a diastereomeric mixture from 1:1 ethyl acetate/cyclohexane as a colourless oil.
LC-MS (System A): Rt = 3.61 and 3.64min. Mass Spectrum *m/z* 508[MH+]

Intermediate 24B

Intermediate 24B was prepared by Synthetic Method C using Intermediate 22 (0.045g) in dry acetonitrile (2ml), phenethyl isocyanate (0.02ml) and triethylamine (0.042ml). The title compound (0.037g) was obtained as a diastereomeric mixture from 1:1 ethyl acetate/cyclohexane as a colourless oil.
LC-MS (System A): Rt = 3.66min. Mass Spectrum *m/z* 522[MH+]

Intermediate 25

Intermediate 25 was prepared in a similar manner to Intermediate 17 using Intermediate 20 (0.303g) in ethanol (10ml), potassium carbonate (0.223g) and

methyl iodide (0.051ml) to give the title compound (0.13g) as a diastereomeric mixture as a yellow oil.
LC-MS (System A): Rt = 2.58min. Mass Spectrum *m/z* 385[MH+]

Intermediate 26
Intermediate 26 was prepared in a similar manner to Intermediate 14 using Intermediate 25 (0.13g) in ethanol (10ml) and 5% aqueous potassium carbonate solution (10ml) to give the title compound (0.098g) as a diastereomeric mixture as a yellow oil.
LC-MS (System A): Rt = 1.85min. Mass Spectrum *m/z* 289[MH+]

Intermediate 27
A solution of β-amino-3,4-benzeneethanol [CAS 188586-38-1] (1.03g) at 80°C was treated with 2,3-epoxypropylphthalimide [CAS5455-98-1] (1.22g) and stirred for 3.5hrs. The mixture was treated with concentrated sulphuric acid (1.7ml) and heated to 150°C for 18hrs, cooled and made alkaline using 2 M sodium hydroxide then extracted three times with ethyl acetate. The mixture was filtered through celite then washed with water, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification on silica (flash column) using 10% methanol/chloroform/1% 880 ammonia solution gave the title compound (0.125g) as a dark brown gum.
LC-MS (System A): Rt = 0.79min. Mass Spectrum *m/z* 261[MH^+]

Intermediate 28
Intermediate 28 was prepared in a similar manner to Intermediate 12 using Intermediate 27 (0.38g) in methanol(30ml) with ethyl trifluoroacetate (0.17g) and triethylamine(0.2ml) to give the title compound (0.32g) as a white solid.
LC-MS (System A): Rt = 2.28min. Mass Spectrum *m/z* 357[MH+].

Intermediate 29
Intermediate 29 was prepared in a similar manner to Intermediate 13 using Intermediate 28 (0.31g), di-tert-butyl dicarbonate(0.23g) and triethylamine(0.30ml) in dichloromethane(10ml) to give the title compound(0.34g) as a colourless gum.
LC-MS (System A): Rt = 3.70min. Mass Spectrum *m/z* 455[MH+].

Intermediate 30
Intermediate 30 was prepared in a similar manner to Intermediate 14 using Intermediate 29 (0.34g) in ethanol(10ml) and potassium carbonate solution(5ml) to give the title compound (0.25g) as a colourless oil

LC-MS (System A): Rt = 2.69min. Mass Spectrum *m/z* 305[MH+] - t-Bu.

Intermediate 31A

Intermediate 31A was prepared by Synthetic Method B using Intermediate 30 (0.05g) in dry dimethylformamide(3ml), benzoic acid(0.016g), HATU(0.05g) and diisopropylethylamine(0.022ml). The title compound (0.09g) was obtained as a colourless oil.

LC-MS (System A): Rt = 3.68min. Mass Spectrum *m/z* 465[MH+].

Intermediate 31B

Intermediate 31B was prepared by Synthetic Method B using Intermediate 30 (0.05g) in dry dimethylformamide(3ml), phenyacetic acid(0.018g), HATU(0.05g) and diisopropylethylamine(0.022ml). The title compound (0.09g) was obtained as a colourless oil.

LC-MS (System A): Rt = 3.67min. Mass Spectrum *m/z* 479[MH+].

Intermediate 31C

Intermediate 31C was prepared by Synthetic Method B using Intermediate 30 (0.05g) in dry dimethylformamide(3ml), phenylpropionic acid(0.02g), HATU(0.05g) and diisopropylethylamine(0.022ml). The title compound (0.08g) was obtained as a colourless oil.

LC-MS (System A): Rt = 3.73min. Mass Spectrum *m/z* 493[MH+].

Intermediate 32A

Intermediate 32A was prepared by Synthetic Method C using Intermediate 30(0.05g), in dry acetonitrile(2ml), benzyl isocyanate(0.02ml), and triethylamine(0.05ml). The title compound (0.06g) was obtained as a colourless gum.

LC-MS (System A): Rt = 3.65min. Mass Spectrum *m/z* 494[MH+].

Intermediate 32B

Intermediate 32B was prepared by Synthetic Method C using Intermediate 30(0.05g), in dry acetonitrile(2ml), phenethyl isocyanate(0.02ml), and triethylamine(0.05ml). The title compound (0.06g) was obtained as a colourless gum.

LC-MS (System A): Rt = 3.69min. Mass Spectrum *m/z* 508[MH+].

Intermediate 33

Intermediate 33 was prepared in a similar manner to Intermediate 12 using Intermediate 27 (0.38g) in methanol(30ml) with ethyl trifluoroacetate (0.17g) and triethylamine(0.2ml) to give the title compound (0.07g) as a pale brown oil.
LC-MS (System A): Rt = 2.36min. Mass Spectrum *m/z* 357[MH+].

Intermediate 34
Intermediate 34 was prepared in a similar manner to Intermediate 13 using Intermediate 33 (0.07g), di-tert-butyl dicarbonate(0.05g) and triethylamine(0.06ml) in dichloromethane(5ml) to give the title compound(0.07g) as a yellow gum.
LC-MS (System A): Rt = 3.71min. Mass Spectrum *m/z* 455[MH+].

Intermediate 35
Intermediate 35 was prepared in a similar manner to Intermediate 14 using Intermediate 34 (0.07g) in ethanol(5ml) and potassium carbonate solution(5ml) to give the title compound (0.05g) as a colourless oil
LC-MS (System A): Rt = 2.63min. Mass Spectrum *m/z* 361[MH+].

Intermediate 36
Intermediate 36 was prepared by Synthetic Method B using Intermediate 35 (0.02g) in dry dimethylformamide(3ml), phenyacetic acid(0.009g), HATU(0.02g) and diisopropylethylamine (0.01ml). The title compound (0.05g) was obtained as a colourless oil.
LC-MS (System A): Rt = 3.67min. Mass Spectrum *m/z* 479[MH+].

Intermediate 37
Intermediate 37 was prepared by Synthetic Method C using Intermediate 30(0.02g), in dry acetonitrile(2ml), benzyl isocyanate(0.008ml), and triethylamine(0.02ml). The title compound (0.03g) was obtained as a colourless gum.
LC-MS (System A): Rt = 3.66min. Mass Spectrum *m/z* 494[MH+].

Intermediate 38
A solution of 3,4-dihydro-2H-1,4-benzoxazine-2-methanamine [CAS102908-68-9] (0.96g) in methanol (20ml) was treated with ethyl trifluoroacetate (0.7ml) and triethylamine (0.81ml) and the resulting solution was left standing at room temperature for 5h. The solution was concentrated *in vacuo* to give the title compound (1.56g) as a yellow solid.
LC-MS (System A): Rt = 2.72 min. Mass Spectrum *m/z* 261[MH+]

Intermediate 39

A solution of Intermediate 38 (1.54g) in dichloromethane (40ml) was treated with 3,4 - dichlorobenzyl bromide (0.85ml) and diisopropylethylamine (1.03ml) and the resulting solution was stirred at room temperature for 5h and left standing overnight. The solution was concentrated *in vacuo*. Chromatographic purification on silica (Biotage™, 90g), eluting with cyclohexane/ethyl acetate (4:1) gave the title compound (1.4g) as a white solid.

LC-MS (System A): Rt = 3.83min. Mass Spectrum *m/z* 419[MH^+]

Intermediate 40

Intermediate 40 was prepared by Synthetic Method E using Intermediate 39 (1.4g) in ethanol (30ml) and 5% aqueous potassium carbonate solution (30ml) to give the title compound (0.85g) as a yellow solid.

LC-MS (System A): Rt = 2.68min. Mass Spectrum *m/z* 323[MH^+]

Intermediate 41

A solution of 2-aminoethyl-4-benzylmorpholine [CAS112914-08-6] (1.8g) in methanol (20ml) was treated with ethyl trifluoroacetate (0.97ml) and triethylamine (1.1ml) and the resulting solution was left overnight. The solution was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 50g), eluting with a gradient of cyclohexane/ethyl acetate, gave the title compound (2.17g) as a colourless oil.

LC-MS (System A): Rt = 1.90 min. Mass Spectrum *m/z* 317[MH+]

Intermediate 42

A solution of Intermediate 41 (2.3g) in ethanol (70ml) was hydrogenated at room temperature and atmospheric pressure, using 10% palladium on activated carbon as the catalyst. On completion, the reaction mixture was filtered through celite and concentrated *in vacuo* to give the title compound (1.56g) as a yellow oil.

LC-MS (System A): Rt = 0.58min. Mass spectrum *m/z* 227[MH+]

Intermediate 43

A solution of Intermediate 42 (1.56g) in dichloromethane (50ml) was treated with di-t-butyl dicarbonate (1.5g) and triethylamine (0.96ml) and the resulting solution was stirred at room temperature for 4h. The solution was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 50g), eluting with a gradient of cyclohexane/ethyl acetate, gave the title compound (2.1g) as a white solid.

LC-MS (System A): Rt = 2.96 min. Mass Spectrum *m/z* 325[MH-]

Intermediate 44

A solution of Intermediate 43 (2.1g) in methanol (50ml) was treated with 5% aqueous potassium carbonate solution (25ml) and the resulting solution was stirred at room temperature for 4h. The solution was concentrated *in vacuo*. The residue was dissolved in dichloromethane (20ml) and sequentially washed with water (20ml), brine (20ml), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (1.12g) as a colourless oil.

LC-MS (System A): Rt = 1.85 min. Mass Spectrum *m/z* 231[MH+]

Intermediate 45

A solution of Intermediate 44 (1.1g) in dichloromethane (100ml) was treated with 3,4-dichlorobenzaldehyde (0.84g) and sodium triacetoxyborohydride (2.5g) and the resulting solution was stirred at room temperature overnight. The reaction mixture was washed with saturated sodium bicarbonate (2x50ml). The aqueous layer was washed with dichloromethane (50ml). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 50g), using a gradient of cyclohexane/ethyl acetate gave the title compound (1.03g) as a colourless oil.

LC-MS (System A): Rt = 2.6min. Mass Spectrum *m/z* 389[MH^+]

Intermediate 46

A solution of Intermediate 45 (0.69g) and triethylamine (0.3ml) in anhydrous dichloromethane at 0°C was treated dropwise with trifluoroacetic anhydride (0.3ml), under nitrogen. The resulting solution was stirred at 0°C for 1h and allowed to warm to room temperature and stirred for a further 4h. The reaction mixture was sequentially washed with saturated sodium bicarbonate (50ml), 2M HCl (50ml), brine (50ml), dried ($Mg SO_4$) and concentrated *in vacuo* to give a yellow oil. Chromatographic purification by SCX (IST Isolute ™, 10g), eluting with methanol gave the title compound (0.68g) as a beige oil.

LC-MS (System A): Rt = 3.91min. Mass Spectrum *m/z* 485[MH^+]

Intermediate 47

A solution of Intermediate 46 (0.68g) in dichloromethane (10ml) was treated with trifluoroacetic acid (5ml) and allowed to stand for 4h at room temperature. The solution was concentrated *in vacuo*. The residue was dissolved in dichloromethane (10ml) and washed with saturated sodium bicarbonate (x2), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (0.52g) as a yellow oil.

LC-MS (System A): Rt = 2.68min. Mass Spectrum *m/z* 385[MH+]

Intermediate 48A

Intermediate 48A was prepared using Synthetic Method B using Intermediate 47 (0.023g) in anhydrous dimethylformamide (4ml), benzoic acid (0.0073g), HATU (0.023g) and diisopropylethylamine (0.01ml). The title compound (0.022g) was obtained as a colourless oil.

LC-MS (System A): Rt = 3.61min. Mass Spectrum *m/z* 489[MH^+]

Intermediate 48B

Intermediate 48B was prepared using Synthetic Method B using Intermediate 47 (0.023g) in anhydrous dimethylformamide (4ml), phenylacetic acid (0.0082g), HATU (0.023g) and diisopropylethylamine (0.01ml). The title compound (0.013g) was obtained as a colourless oil.

LC-MS (System A): Rt = 3.66min. Mass Spectrum *m/z* 503[MH^+]

Intermediate 48C

Intermediate 48C was prepared using Synthetic Method B using Intermediate 47 (0.023g) in anhydrous dimethylformamide (4ml), hydrocinnamic acid (0.009g), HATU (0.023g) and diisopropylethylamine (0.01ml). The title compound (0.017g) was obtained as a colourless oil.

LC-MS (System A): Rt = 3.73min. Mass Spectrum *m/z* 517[MH^+]

Intermediate 49A

Intermediate 49A was prepared by Synthetic Method C using Intermediate 47 (0.055g) in dry acetonitrile (6ml), benzyl isocyanate (0.021ml) and triethylamine (0.05ml). The title compound (0.032g) was obtained as a colourless oil.

LC-MS (System A): Rt = 3.65min. Mass Spectrum *m/z* 518[MH^+]

Intermediate 49B

Intermediate 49B was prepared by Synthetic Method C using Intermediate 47 (0.055g) in dry acetonitrile (6ml), phenethyl isocyanate (0.024ml) and triethylamine (0.05ml). The title compound (0.039g) was obtained as a colourless oil.

LC-MS (System A): Rt = 3.68min. Mass Spectrum *m/z* 532[MH^+]

Intermediate 50

A solution of Intermediate 45 (0.5g) in dichloromethane (40ml) was treated with paraformaldehyde (0.5g), glacial acetic acid (0.2ml) and sodium triacetoxyborohydride (0.68g) and stirred at room temperature for 3 days. The reaction mixture was sequentially washed with saturated sodium bicarbonate

(2x50ml), brine (50ml), dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 20g), using a gradient of cyclohexane/ethyl acetate gave the title compound (0.3g) as a colourless oil.

LC-MS (System A): Rt = 2.67min. Mass Spectrum *m/z* 403[MH^+]

Intermediate 51

A solution of Intermediate 50 (0.3g) in dichloromethane (10ml) was treated with trifluoroacetic acid (10ml) and allowed to stand for room temperature overnight. The solution was concentrated *in vacuo*. The residue was dissolved in dichloromethane (10ml) and washed with saturated sodium bicarbonate (x2), dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (0.22g) as a colourless oil.

LC-MS (System A): Rt = 1.64min. Mass Spectrum *m/z* 303[MH+]

Intermediate 52

Intermediate 52 was prepared in a similar manner to Intermediate 45 using *tert*-butyl 2-(aminomethyl)-morpholine-4-carboxylate [140645-53-0] (1g) in dichloromethane(30ml), 3,4-dichlorobenzaldehyde(0.97g) and sodium triacetoxyborohydride (2.45g) to give the title compound(1.32g) as a colourless gum.

LC-MS (System A): Rt = 2.50min. Mass Spectrum *m/z* 375[MH+].

Intermediate 53

Intermediate 53 was prepared in a similar manner to Intermediate 50 using Intermediate 52(1.3g) in dichloromethane(75ml), paraformaldehyde(1.3g), sodium triacetoxyborohydride(1.83g) and glacial acetic acid(0.5ml) to give the title compound (1.34g) as a colourless oil.

LC-MS (System A): Rt = 2.57min. Mass Spectrum *m/z* 389[MH+].

Intermediate 53A

A stirred solution of Intermediate 52(1.36g) in dichloromethane(80ml) and triethylamine(1.8ml)at 0°C under N_2 was treated with trifluoroacetic anhydride(0.77ml) dropwise. The mixture was stirred at 0°C for 1hr then after 2hrs at room temp it was washeh with a saturated solution of sodium hydrogen carbonate(50ml),2M hydrochloric acid(50ml) saturated sodium chloride(50ml), dried over magnesium sulphate, filtered and evaporated. Chromatographic purification on silica (Varian Bond-Elut™, 50g), eluting with a gradient of cyclohexane/ ethyl acetate gave the title compound (1.66g) from 4:1 cyclohexane/ethyl acetate as a pale yellow viscous gum.

LC-MS (System A): Rt = 3.93min. Mass Spectrum *m/z* 471[MH+].

Intermediate 54
Intermediate 54 was prepared in a similar manner to Intermediate 51 using Intermediate 53(1.32g) in a 1:1 mixture of dichloromethane/trifluoroacetic acid (20ml) to give the title compound(0.95g) as a colourless oil.
LC-MS (System A): Rt = 0.93min. Mass Spectrum *m/z* 289[MH+].

Intermediate 54A
Intermediate 54A was prepared in a similar manner to Intermediate 51 using Intermediate 53A (1.64g) in a 1:1 mixture of dichloromethane/Trifluoroacetic acid (20ml) to give the title compound(0.95g) as a colourless oil.
LC-MS (System A): Rt = 2.54min. Mass Spectrum *m/z* 371[MH+].

Intermediate 55A
Intermediate 55A was prepared by Synthetic Method B using Intermediate 54A(0.076g), in dry dimethylformamide(3ml), benzoic acid(0.025g), HATU(0.078g) and diisopropylethylamine(0.036ml). The title compound (0.079g) was obtained from 1:1 cyclohexane/ethyl acetate as a colourless oil.
LC-MS (System A): Rt = 3.64min. Mass Spectrum *m/z* 475[MH+].

Intermediate 55B
Intermediate 55B was prepared by Synthetic Method B using Intermediate 54A(0.076g), in dry dimethylformamide(3ml), phenylacetic acid(0.028g), HATU(0.078g) and diisopropylethylamine(0.036ml). The title compound (0.070g) was obtained from 1:1 cyclohexane/ethyl acetate as a colourless oil.
LC-MS (System A): Rt = 3.67min. Mass Spectrum *m/z* 490[MH+].

Intermediate 55C
Intermediate 55C was prepared by Synthetic Method B using Intermediate 54A(0.076g), in dry dimethylformamide(3ml), 3-phenylpropionic acid(0.031g), HATU(0.078g) and diisopropylethylamine(0.036ml). The title compound (0.075g) was obtained from 1:1 cyclohexane/ethyl acetate as a colourless oil.
LC-MS (System A): Rt = 3.76min. Mass Spectrum *m/z* 503[MH+].

Intermediate 56A
Intermediate 56A was prepared by Synthetic Method C using Intermediate 54A(0.076g), in dry acetonitrile(2ml), benzyl isocyanate(0.030ml), and triethylamine(0.071ml). The title compound (0.10g) was obtained from 1:1 cyclohexane/ethyl acetate as a colourless gum.
LC-MS (System A): Rt = 3.66min. Mass Spectrum *m/z* 504[MH+].

Intermediate 56B

Intermediate 56B was prepared by Synthetic Method C using Intermediate 54A(0.076g), in dry acetonitrile(2ml), phenethyl isocyanate(0.034ml), and triethylamine(0.071ml). The title compound (0.097g) was obtained from 1:1 cyclohexane/ethyl acetate as a colourless gum.
LC-MS (System A): Rt = 3.71min. Mass Spectrum *m/z* 518[MH+].

Intermediate 57

A solution of *cis*-pyrrolo[3,4-b]-1,4-oxazine-6(2H)-carboxylic acid, hexahydro-, 1,1-dimethylethyl ester [138027-02-8] (0.28g) in anhydrous dichloromethane(10ml) was treated with triethylamine(0.26ml) and 3,4-dichlorobenzyl bromide(0.19ml) and stirred at room temp for 18hrs. The mixture was washed with a saturated solution of sodium hydrogen carbonate(10ml) and the organic phase was separated through a hydrophobic frit and concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 10g), eluting with a gradient of cyclohexane /ethyl acetate gave the title compound (0.16g) from 4:1 cyclohexane/ethyl acetate as a colourless oil.
LC-MS (System A): Rt = 3.67min. Mass Spectrum *m/z* 387[MH+].

Intermediate 58

Intermediate 57 was treated with a 1:1 mixture of dichloromethane/trifluoroacetic acid (6ml) at room temp for 2.5hrs. The mixture was concentrated *in vacuo* and partitioned between dichloromethane (20ml) and saturated sodium hydrogen carbonate solution(20ml), separated the organic phase through a hydrophobic frit and concentrated *in vacuo* to give the title compound (0.092g) as a reddish gum.
LC-MS (System A): Rt = 2.37min. Mass Spectrum *m/z* 287[MH+].

Intermediate 59

A mixture of CBZ-pyrrolidine 3,4-epoxide [CAS 31865-25-5] (3.95g) and N-(3,4-dichlorobenzyl)ethanolamine [CAS 40172-06-3] (5.60g) in ethanol (30ml) was heated at reflux for 20h. The solvent was removed *in vacuo*. Chromatographic purification of the residue on silica (90g Biotage), eluting with a gradient of cyclohexane/ethyl acetate, gave the title compound (1.09g) as a pale yellow oil.
LC-MS (System A): Rt = 3.19min. Mass Spectrum *m/z* 438[MH^+]

Intermediate 60

Triphenylphosphine (0.77g) was added to a stirred solution of Intermediate 59 (1.07g) in tetrahydrofuran (15ml). The solution was cooled to 0° and treated with diisopropylazodicarboxylate (0.58ml). The reaction mixture was warmed to room

temperature and stirred at room temperature for 4h. The solvent was removed *in vacuo*. Chromatographic purification of the residue on silica (90g Biotage), eluting with a (1:1) mixture of cyclohexane and ethyl acetate, gave a solid. Further purification on silica (Varian SCX Bond-Elut™, 3x10g), eluting with 1% ammonia in methanol, gave the title compound (0.69g) as a white foam.
LC-MS (System A): Rt = 3.78min. Mass Spectrum *m/z* 421[MH^+]

Intermediate 61

A solution of boron tribromide in dichloromethane (1.0M, 2.3ml) was added, dropwise, to a stirred solution of Intermediate 60 (0.20g) in dichloromethane (18ml), at 0-5° under nitrogen. The reaction mixture was stirred at 0-5° for 0.5h then warmed to room temperature over 1.75h. Methanol (3ml) was added, with vigorous stirring. The resultant suspension was stirred for 0.5h. The solvents were removed *in vacuo*. The residual solid was triturated in diethyl ether (2x15ml) over 0.5h. The solvent was decanted and the solid residue was partitioned between ethyl acetate (2x30ml) and 0.4M sodium bicarbonate. The aqueous phase was saturated with sodium chloride and further extracted with ethyl acetate (2x25ml + 2x50ml). All the ethyl acetate extracts were combined, dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (0.11g) as a pale brown gum.
LC-MS (System A): Rt = 2.24min. Mass Spectrum *m/z* 287[MH^+]

Intermediate 62

A solution of DL-serine [CAS 302-84-1] (6.22g) in dimethylformamide (200ml) was treated with 3,4-dichlorobenzaldehyde (7.0g), diisopropylethylamine (7.0ml), glacial acetic acid (1.0ml) and a portionwise addition of sodium triacetoxyborohydride (13g), stirred at room temperature for 3hrs and concentrated *in vacuo*. The residue was treated with water (120ml) and extracted with ethyl acetate (200ml), dried (Na_2SO_4) and concentrated *in vacuo*. Chromatographic purification on silica (90g Biotage), using a gradient of cyclohexane/ethyl acetate gave the title compound (6.4g) as a white solid.
LC-MS (System A): Rt = 2.11min. Mass Spectrum *m/z* 278[MH^+]

Intermediate 63

A solution of intermediate 62 (6.38g) in methanol (200ml) was treated with 2M sodium hydroxide solution (50ml) and the mixture heated at reflux for 17hrs. The mixture was concentrated *in vacuo* and the residue taken up in water (250ml), extracted with ether (60ml) and the aqueous acidified to pH4 using concentrated hydrochloric acid and cooled on ice when the title compound (4.47g) crystallised as a white solid.

Intermediate 64

A solution of intermediate 63 (4.44g) in water (25ml) and sodium hydroxide (0.826g) was cooled on ice. The mixture was stirred vigorously and chloroacetyl chloride (1.77ml) was added slowly over 1hr. After 0-5hr at 0-5°C sodium hydroxide (1.3g) in water (4ml) was added and the mixture stirred at room temperature for 17hrs then heated to 40°C for 2hrs. The mixture was extracted with ether (15ml) and the aqueous phase acidified using concentrated hydrochloric acid then extracted with ethyl acetate (80ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (4.37g) as a white solid.
LC-MS (System A): Rt = 3.01min. Mass Spectrum *m/z* 302[MH^-].

Intermediate 65

A solution of intermediate 64 (4.35g) in tetrahydrofuran (100ml) was treated with carbonyldiimidazole (2.48g) and stirred under nitrogen at room temperature for 1hr. 880 ammonia solution (5ml) was added and stirred at room temperature for 4hrs. The mixture was concentrated *in vacuo* and the residue partitioned between ethyl acetate/2 M hydrochloric acid (100ml) washed with 8% sodium bicarbonate (100ml) dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (1.417g) as a white solid.
LC-MS (System A): Rt = 2.59min. Mass Spectrum *m/z* 301[MH^-]

Intermediate 66

A suspension of Intermediate 65 (1.41g) in anhydrous tetrahydrofuran (100ml) under nitrogen was treated with borane-tetrahydrofuran complex (10ml) and heated to reflux for 17hrs. The mixture was cautiously quenched by the slow addition of methanol (20ml). 6 M hydrochloric acid (30ml) was added and the mixture heated to reflux for 3hrs and concentrated *in vacuo*. The residue was partitioned between ethyl acetate (100ml) and 8% sodium bicarbonate (150ml) dried (Na_2SO_4) and concentrated *in vacuo*. Chromatographic purification on silica (90g Biotage), using a gradient of dichloromethane/methanol/880 ammonia gave the title compound (0.52g) as a colourless oil.
LC-MS (System A): Rt = 2.22min. Mass Spectrum *m/z* 275[MH^+]

Intermediate 67

A suspension of Intermediate 64 (5.0g) in chloroform (125ml) under nitrogen, was treated with thionyl chloride (10ml) and heated at reflux for 17hrs. Concentration *in vacuo* and co-evaporation with chloroform gave a residue which was dissolved in 1:1acetonitrile/tetrahydrofuran (40ml), cooled on ice under nitrogen, and treated with 2 M (trimethylsilyl)diazomethane in hexane (20ml). The

mixture was allowed to stand at 0-5°C for 24hrs then concentrated *in vacuo*. The residue was dissolved in collidine (20ml) and added dropwise, over 5min, to a solution of benzyl alcohol (20ml) in collidine (20ml) at 180°C. The mixture was stirred for 10min, cooled and concentrated *in vacuo* and the residue partitioned between ethyl acetate (300ml) and 5 M hydrochloric acid (120ml). The organics washed with 8% sodium bicarbonate (150ml), dried (Na_2SO_4) and concentrated *in vacuo*. Chromatographic purification on silica (90g Biotage), eluting with a gradient of cyclohexane/diethyl ether gave the title compound (2.317g) as a pale yellow gum.
LC-MS (System A): Rt = 3.46min. Mass Spectrum *m/z* 408[MH^+]

Intermediate 68
A mixture of Intermediate 67 (2.05g) and lithium hydroxide (1.00g) in tetrahydrofuran (50ml) and water (25ml) was stirred for 24h, concentrated to 10ml *in vacuo* and partitioned between ethyl acetate (75ml) and water (75ml). The aqueous phase was separated, made acidic with 10% w/v citric acid solution and the resultant suspension extracted with ethyl acetate (100ml). These extracts were dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (1.36g) as a waxy, pale brown solid.
LC-MS (System A): Rt = 2.79min. Mass Spectrum *m/z* 318[MH^+]

Intermediate 69
A solution of Intermediate 68 (1.36g) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (2.11g) in acetonitrile (50ml) was stirred for 10min then treated with a 0.5M solution of ammonia in dioxan (17ml). The reaction mixture was stirred for 22h, more 0.5M ammonia in dioxan (9ml) being added after 4h. The reaction mixture was concentrated to 5ml *in vacuo* then partitioned between ethyl acetate (100ml) and 0.5M sodium bicarbonate (100ml). The organic phase was separated, washed with 5% w/v citric acid (100ml) and water (50ml), dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (1.07g) as a pale brown gum.
LC-MS (System A): Rt = 2.54min. Mass Spectrum *m/z* 317[MH^+]

Intermediate 70
Borane-tetrahydrofuran complex (1.0M in tetrahydrofuran, 27ml) was added, in a slow stream over 5 min, to a stirred solution of Intermediate 69 (1.06g) in tetrahydrofuran (75ml). The reaction mixture was stirred and heated to reflux then heated at reflux for 24h, cooled to room temperature and treated, rapidly dropwise with stirring, with methanol (25ml). After stirring for 1h, 4M hydrochloric acid (25ml) was added. The solution was stirred for a further 0.5h, left to stand

overnight then concentrated to 20ml *in vacuo*. The resultant suspension was made basic with 1M sodium bicarbonate and extracted with ethyl acetate (3x75ml). The combined organics were dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (0.72g) as a colourless gum.
LC-MS (System A): Rt = 1.85min. Mass Spectrum *m/z* 289[MH^+]

Intermediate 71
A solution of 2-(3,4-dichloro-benzylamine)-ethanol [CAS 40172-06-3] (0.638g) in anhydrous tetrahydrofuran (40ml) was treated with sodium hydride 60% dispersion in oil (0.232g) and allowed to stir at room temperature for 30mins, followed by portionwise addition of a solution of ethyl-3-(bromomethyl)-propionate [CAS 58539-11-0] (0.46ml) in anhydrous tetrahydrofuran (20ml). The resulting mixture was stirred at room temperature for 1.5h. The reaction was quenched by addition of water (50ml) and extracted into dichloromethane (50ml). The organic layer was washed with water, dried ($MgSO_4$) and concentrated *in vacuo* to give the title compound (0.987g) as a yellow oil.
LC-MS (System A): Rt = 2.37 min. Mass Spectrum *m/z* 332[MH+]

Intermediate 72
A solution of Intermediate 71 (0.98g) in anhydrous tetrahydrofuran (270ml) was treated with sodium hydride 60% dispersion in mineral oil (0.116g) and the resulting mixture was stirred at room temperature, under nitrogen, overnight. The reaction was quenched by the addition of saturated ammonium chloride solution (100ml) and water (50ml). The organic layer was separated and the aqueous was extracted with dichloromethane (50ml). The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 20g), using a gradient of cyclohexane/ethyl acetate gave the title compound (0.189g) as a yellow oil.
LC-MS (System A): Rt = 2.5min. Mass Spectrum *m/z* 332[MH^+]

Intermediate 73
A solution of Intermediate 72 (0.183g) in ethanol (5ml) was treated with 2M sodium hydroxide (5ml) and the resulting solution was stirred at room temperature for 2h. The reaction mixture was acidified with citric acid solution to pH 6 and extracted into dichloromethane. The aqueous layer was washed with dichloromethane and the combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo* to give the title compound (0.145g) as a colourless oil.
LC-MS (System A): Rt = 2.04 min. Mass Spectrum *m/z* 304[MH+]

Intermediate 74

Intermediate 74 was prepared using Synthetic Method B using Intermediate 73 (0.145g) in anhydrous dimethylformamide (20ml), 0.5M ammonia in dioxan (4.8ml) and HATU (0.181g). The title compound (0.118g) was obtained as a yellow oil.
LC-MS (System A): Rt = 1.83min. Mass Spectrum *m/z* 303[MH^+]

Intermediate 75
A solution of Intermediate 74 (0.118g) in anhydrous tetrahydrofuran (10ml) was treated with a 1.0M solution of borane/THF complex in THF (1.95ml) and the resulting mixture was heated under reflux for 5h. The mixture was quenched with methanol (10ml) and 2M hydrogen chloride (5ml) and concentrated *in vacuo*. The residue was dissolved in methanol (10ml) and 0.5M ammonia in dioxan (10ml) and concentrated *in vacuo*. Chromatographic purification by SCX (IST Isolute ™, 5g), eluting with methanol and 10%ammonia/methanol gave the title compound (0.10g) as a colourless oil.
LC-MS (System A): Rt = 1.61min. Mass Spectrum *m/z* 289[MH^+]

Intermediate 76
A solution of ethyl 4-oxotetrahydro-2H-pyran-2-carboxylate [CAS 287193-07-1] (4.0g) in ethanol (40ml) was treated with pyridine (4ml) and hyrroxylamine hydrochloride (4.0g). The mixture was heated at 65°C for 1hr then concentrated *in vacuo*. The residue was taken up in water (20ml) and saturated with potassium carbonate then extracted with dichloromethane, dried ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification on silica (90g Biotage), using 1:1 ethyl acetate/cyclohexane gave the title compound (3.0g) as a colourless oil.
LC-MS (System A): Rt = 1.74min. Mass Spectrum *m/z* 188[MH^+]

Intermediate 77
To intermediate 76 (3.0g) under nitrogen was added polyphosphoric acid (20g) and the mixture heated at 115°C for 30mins when ice/water was added. The mixture was extracted with chloroform (3x100ml) dried ($MgSO_4$) and concentrated *in vacuo*. Chromatographic purification on silica silica (Varian Bond-Elut™, 20g), eluting with a gradient of ethyl acetate/cyclohexane then 10%methanol/ethyl acetate gave the title compound (0.9g) as a pale brown oil.
LC-MS (System A): Rt = 1.47min. Mass Spectrum *m/z* 188[MH^+]

Intermediate 78
A solution of Intermediate 77 (0.7g) in anhydrous tetrahydrofuran (20ml) under nitrogen, was added borane-tetrahydrofuran complex (20ml) and the mixture heated to 65°C for 18hrs. The mixture was carefully quenched using methanol

(5ml) then 2 M hydrochloric acid (20ml) and concentrated *in vacuo*. The residue was taken up in methanol (20ml) treated with 0.5 M ammonia in 1,4-dioxane (20ml) and concentrated *in vacuo*. Repeated addition of methanol (3x20ml) and concentration *in vacuo* gave a residue which was purified by SCX (IST Isolute ™, 2x10g), eluting with methanol and 10% 880 ammonia/methanol to give the title compound (0.49g) as a colourless oil.
LC-MS (System A): Rt = 1.43min. Mass Spectrum *m/z* 132[MH^+]

Intermediate 79

A solution of Intermediate 78 (0.49g) in anhydrous dichloromethane (30ml) was added triethylamine (0.52ml) and 3,4-dichlorobenzyl bromide (0.54ml) and the mixture stirred at 20°C for 3hrs. Chromatographic purification on silica (Varian Bond-Elut™, 20g), eluting with a gradient of ethyl acetate/cyclohexane then 10%methanol/ethyl acetate gave the title compound (0.87g) as a colourless oil.
LC-MS (System A): Rt = 1.65min. Mass Spectrum *m/z* 290[MH^+]

Intermediate 80

A solution of Intermediate 79 (0.52g) in anhydrous chloroform (15ml) was treated with thionyl chloride (0.26ml) and the mixture heated to reflux for 3hrs. The cooled mixture was washed with 10% sodium bicarbonate solution, dried ($MgSO_4$) concentrated *in vacuo* and dissolved in anhydrous dimethylformamide (10ml) and treated with sodium azide (0.226g), heated to 130°C for 2 hours then concentrated *in vacuo*. The mixture was partitioned between 10% sodium bicarbonate solution and dichloromethane, dried ($MgSO_4$) concentrated *in vacuo* to give the title compound (0.23g) as a pale brown oil. LC-MS (System A): Rt = 2.33min. Mass Spectrum *m/z* 315[MH^+]

Intermediate 81

A solution of Intermediate 80 (0.22g) in anhydrous toluene (10ml) at 0°C was treated, dropwise, with sodium bis(2-methoxyethoxy0aluminium hydride 65+ wt. % in toluene (0.42ml) and warmed to room temperature for 1 hour. The mixture was quenched at 0°C by cautious addition of water followed by 48% sodium hydroxide, separated and dried ($MgSO_4$). Concentrated *in vacuo* to give the title compound (0.19g) as a colourless oil.
LC-MS (System A): Rt = 1.33min. Mass Spectrum *m/z* 289[MH+]

Intermediate 82

A solution of methyl 3-carboxyphenyl acetate [CAS 113496-14-3] (0.89g) in toluene (40ml) was treated with thionyl chloride (10ml) and the resulting solution was heated at 85°C under nitrogen for 2h. Concentration *in vacuo* and co-

evaporation with dichloromethane gave a residue which was dissolved in dichloromethane (10ml) and treated with cyclopropylamine (1.7ml). The mixture was left standing overnight at room temperature and then concentrated *in vacuo*. The residue was dissolved in ethyl acetate and sequentially washed with saturated sodium bicarbonate solution, water, 1M hydrochloric acid, brine, dried (Na_2SO_4) and concentrated *in vacuo* to give the title compound (0.805g) as an oil, which solidified on standing.
LC-MS (System A): Rt = 2.4min. Mass Spectrum *m/z* 234[MH+]

Intermediate 83
A solution of Intermediate 82 (0.8g) in ethanol (10ml) was treated with 2N sodium hydroxide (10ml) and the resulting solution was heated at 75°C under nitrogen for 2h. The mixture was concentrated *in vacuo* and the residue was diluted with water (25ml) and washed with ethyl acetate. The aqueous layer was acidified with 2N hydrochloric acid (10ml) and extracted with ethyl acetate (x2). The combined organics were washed with water (x2), brine, dried (Na_2SO_4) and concentrated *in vacuo*. The residue was triturated with ether to give the title compound (0.334g) as a white solid.
LC-MS (System A): Rt = 2.1min. Mass Spectrum *m/z* 220[MH+]

Intermediate 84
Intermediate 84 was prepared in a similar manner to Intermediate 82 using methyl 4-carboxyphenyl acetate [CAS 87524-66-1] (0.455g) in toluene (20ml), thionyl chloride (5ml) and cycloproylamine (0.83ml). Trituration with ether gave the title compound (0.22g) as a white solid.
LC-MS (System A): Rt = 2.32min. Mass Spectrum *m/z* 234[MH+]

Intermediate 85
Intermediate 85 was prepared in a similar manner to Intermediate 83 using Intermediate 84 (0.2g) in ethanol (4ml) and 2N sodium hydroxide (4ml) to give the title compound (0.082g) as a white solid.
LC-MS (System A): Rt = 2.1min. Mass Spectrum *m/z* 220[MH+]

Examples

Example 1
Synthetic Method B
A solution of phenylacetic acid [CAS 103-82-2] (0.0187g) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (HATU) (0.052g), in anhydrous dimethylformamide (2ml) was left standing at room temperature for 5min. Intermediate 5 (0.04g) and diisopropylethylamine

(0.024ml) were added. The resulting mixture was left standing at room temperature for18hrs. The solvent was removed *in vacuo* and the residue partitioned between 10% sodium bicarbonate /dichloromethane separated and dried ($MgSO_4$). Chromatographic purification on silica (Varian Bond-Elut™, 2g), eluting with 1:4 ethyl acetate/cyclohexane, gave the title compound (0.04g) as a colourless gum.
LC-MS (System A): Rt = 2.79min. Mass Spectrum *m/z* 409[MH^+]

Example 6

Synthetic Method A

A solution of 4-Nitrophenyl chloroformate (0.152g) in anhydrous dichloromethane (10ml) at 0°C was treated, dropwise, with a solution of Intermediate 5 (0,22g) and triethylamine (0.105ml) in anhydrous dichloromethane (5ml). After stirring at room temperature for 18hrs the mixture was concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 10g), eluting with a gradient of ethyl acetate/cyclohexane gave Intermediate 5A (0.3g) as a pale yellow gum. Benzylamine [CAS 100-46-9] in anhydrous acetonitrile (2ml) was treated with Intermediate 5A (0.04g) and diisopropylethylamine (0.03ml). The mixture was stirred for 18hrs and purified by SCX (IST Isolute ™, 1g), eluting with methanol and 10% 880 ammonia/methanol to give the title compound (0.033g) as a colourless oil.
LC-MS (System A): Rt = 2.72min. Mass Spectrum *m/z* 424[MH^+]

Example 10

Synthetic Method C

A solution of intermediate 10 (0.032g) in anhydrous dichloromethane (3ml) was treated with triethylamine (0.022ml) and benzyl isocyanate (0.007ml) and stirred at room temperature for 18hrs. Chromatographic purification on silica (Varian Bond-Elut™, 1g), eluting with ethyl acetate gave the title compound (0.02g) as a colourless gum.
LC-MS (System A): Rt = 3.29min. Mass Spectrum *m/z* 456[MH^+]

Example 42

Synthetic Method A

A solution of phenethylamine (0.012g) and diisopropylethylamine (0.020g) in acetonitrile (1ml) was added, dropwise, to a stirred solution of 4-nitrophenyl chloroformate (0.020g) in acetonitrile (1ml). The solution was stirred for 1.75h then treated with a solution of Intermediate 70 (0.023g) in acetonitrile (1ml). The reaction mixture was stirred for 5h then left to stand overnight. The solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate (20ml) and

1M sodium carbonate (20ml). The organic phase was separated, washed with 0.5M sodium carbonate (2x20ml) and water (20ml), dried (Na_2SO_4) and concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 10g), eluting with ethyl acetate, gave the title compound (0.017g) as a colourless gum.
LC-MS (System A): Rt = 2.69min. Mass Spectrum *m/z* 436[MH^+]

Example 44
Synthetic Method B
A solution of benzoic acid (0.012g) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (0.038g) in acetonitrile (3ml) was stirred for 5min then treated with a solution of Intermediate 70 (0.023g) and diisopropylethylamine (0.026g) in acetonitrile (2ml). The reaction mixture was stirred for 6h then left to stand overnight. The solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate (30ml) and 0.5M sodium bicarbonate (25ml). The organic phase was separated, washed with water (25ml), dried (Na_2SO_4) and concentrated *in vacuo* to give a gum. A stirred solution of the gum in diethyl ether (7ml) and ethyl acetate (0.75ml) was treated, dropwise, with 1.0M ethereal hydrogen chloride (0.2ml). The resultant suspension was stirred for 2 min. The solvents were decanted. The residue was washed with diethyl ether and dried *in vacuo* to give the title compound (0.030g) as a cream powder.
LC-MS (System A): Rt = 2.62min. Mass Spectrum *m/z* 393[MH^+]

The starting material for Examples 42-45 may be prepared according to Intermediates 67-70 above.

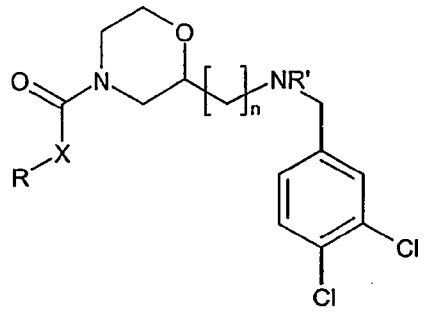
Example 78
Synthetic Method B
A solution of benzoic acid (0.010g) and O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate (0.030g) in acetonitrile (3ml) was stirred for 5min then treated with a solution of Intermediate 61 (0.015g) and diisopropylethylamine (0.020g) in acetonitrile (1ml). The reaction mixture was stirred for 2h then left to stand overnight. The solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate (25ml) and 0.5M sodium bicarbonate (20ml). The organic phase was separated, washed with water (20ml), dried (Na_2SO_4) and concentrated *in vacuo* to give a gum. A stirred solution of the gum in diethyl ether (5ml) and ethyl acetate (1ml) was treated, dropwise, with 1.0M ethereal hydrogen chloride (0.15ml). The resultant suspension was stirred for 5 min. The solvents were decanted. The residue was

washed with diethyl ether and dried *in vacuo* to give the title compound (0.020g) as a cream powder.
LC-MS (System A): Rt = 3.33min. Mass Spectrum *m/z* 391[MH^+]

The starting material for Examples 78-82 may be prepared according to Intermediates 59-61 above.

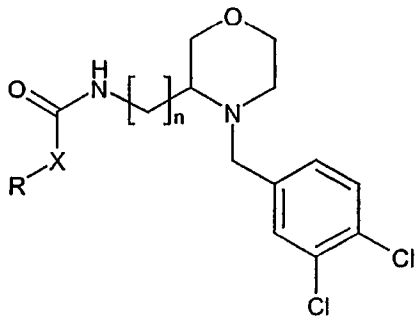
Example 81
Synthetic Method A
A solution of phenethylamine (0.012g) and diisopropylethylamine (0.020g) in acetonitrile (1ml) was added, dropwise, to a stirred solution of 4-nitrophenyl chloroformate (0.020g) in acetonitrile (1ml). The solution was stirred for 1.25h then treated with a solution of Intermediate 61 (0.020g) in acetonitrile (1ml). The reaction mixture was stirred for 3h then left to stand overnight. The solvent was removed *in vacuo*. The residue was partitioned between ethyl acetate (25ml) and 0.5M sodium carbonate (20ml). The organic phase was separated, washed with 0.5M sodium carbonate (20ml), 0.25M sodium carbonate (20ml) and water (20ml), dried (Na_2SO_4) and concentrated *in vacuo*. Chromatographic purification on silica (Varian Bond-Elut™, 5g), eluting with a (1:1) mixture of cyclohexane and ethyl acetate and then with ethyl acetate, gave the title compound (0.021g) from ethyl acetate as a colourless gum.
LC-MS (System A): Rt = 3.44min. Mass Spectrum *m/z* 434[MH^+]

Table A



Ex.	From Int No.	Synthetic Method	R	X	R'	n	LCMS [M+H]+ observed	HPLC R_t (min)
17	54	B	Ph	bond	Me	1	393	2.43
18	54	B	$PhCH_2$	bond	Me	1	407	2.48
19	54	B	$Ph(CH_2)_2$	bond	Me	1	421	2.61
20	54	C	$PhCH_2$	NH	Me	1	422	2.51
21	54	C	$Ph(CH_2)_2$	NH	Me	1	436	2.56
22	55C	E	$Ph(CH_2)_2$	bond	H	1	407	2.57
23	55B	E	$PhCH_2$	bond	H	1	393	2.46
24	56A	G	$PhCH_2$	NH	H	1	408	2.40
25	56B	G	$Ph(CH_2)_2$	NH	H	1	422	2.53
26	55A	E	Ph	bond	H	1	379	2.37
27	51	C	$PhCH_2$	NH	Me	2	436	2.57
28	51	C	$Ph(CH_2)_2$	NH	Me	2	450	2.64
29	49B	G	$Ph(CH_2)_2$	NH	H	2	436	2.58
30	49A	G	$PhCH_2$	NH	H	2	422	2.52
31	51	B	Ph	bond	Me	2	407	2.52
32	51	B	$PhCH_2$	bond	Me	2	421	2.58
33	51	B	$Ph(CH_2)_2$	bond	Me	2	435	2.66
34	48A	E	Ph	bond	H	2	393	2.46
35	48B	E	$PhCH_2$	bond	H	2	407	2.51
36	48C	E	$Ph(CH_2)_2$	bond	H	2	421	2.6

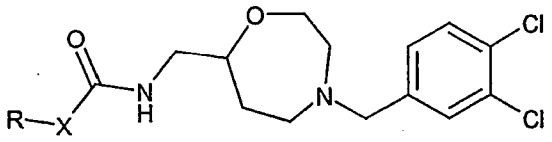
Table B



Ex.	From Int. No.	Synthetic Method	R	X	n	LCMS [M+H]+ observed	HPLC R_t (min)
37	66	A	$PhCH_2$	NH	1	408	2.74
38	66	A	$Ph(CH_2)_2$	NH	1	422	2.82
39	66	B	Ph	bond	1	379	2.94
40	66	B	$PhCH_2$	bond	1	393	3.05
41	66	B	$Ph(CH_2)_2$	bond	1	407	3.09
42	70	A	$Ph(CH_2)_2$	NH	2	436	2.69
43	70	A	$PhCH_2$	NH	2	422	2.62
44*	70	B	Ph	bond	2	393	2.62
45*	70	B	$PhCH_2$	bond	2	407	2.66

5 * hydrochloride

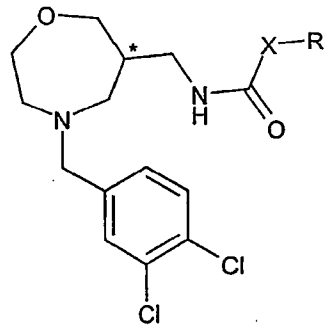
Table B1



Ex.	From Int. No.	Synthetic Method	R	X	LC Rt (min)	LCMS [M+H]+ observed
90	81	C	$PhCH_2$	NH	2.37	422
91	81	C	Ph	NH	2.48	408
92	81	C	$Ph(CH_2)_2$	NH	2.55	436
93	81	B	$PhCH_2$	bond	2.41	407

5

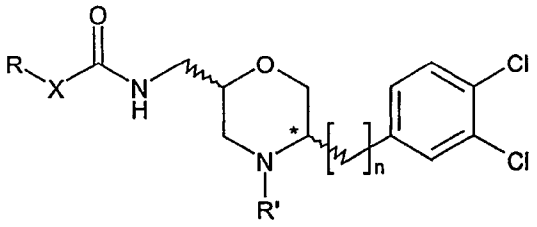
Table B2



Ex.	From Int. No.	Synthetic Method	R	Stereochem.	X	LCMS [M+H]+ observed	HPLC R_t (min)
88	75	B	$PhCH_2$	RS	bond	407	2.34
88A	75	B	$PhCH_2$	R or S	bond	407	2.28
88B	75	B	$PhCH_2$	S or R	bond	407	2.29
89	75	C	$PhCH_2$	RS	NH	422	2.38
89A	75	C	$PhCH_2$	R or S	NH	422	2.32
89B	75	C	$PhCH_2$	S or R	NH	422	2.33
94	75	C	Ph	RS	NH	408	2.41
95	75	C	$Ph(CH_2)_2$	RS	NH	436	2.48

5

Table C



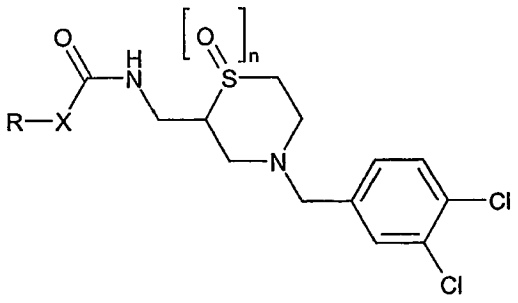
Ex.	From Int. No.	Synthetic Method	R	X	R'	Stereochem at position "*"	n	LCMS [M+H]+ observed	HPLC R_t (min)
50	32C	F	$Ph(CH_2)_2$	NH	H	RS	0	408	2.56
51	32A	F	$PhCH_2$	NH	H	R or S	0	394	2.47
52	37	F	$PhCH_2$	NH	H	S or R	0	394	2.48
53	31C	D	$Ph(CH_2)_2$	bond	H	RS	0	393	2.55
54	31B	D	$PhCH_2$	bond	H	R or S	0	379	2.46
55	36	D	$PhCH_2$	bond	H	S or R	0	379	2.47
56	31A	D	Ph	bond	H	RS	0	365	2.44

Ex.	From Int. No.	Synthetic Method	R	X	R'	Stereochem at position "*"	n	LCMS [M+H]+ observed	HPLC R_t (min)
57	15A	D	Ph	bond	H	S	1	379	2.56
58	15B	D	$PhCH_2$	bond	H	S	1	393	2.60
59	15C	D	$Ph(CH_2)_2$	bond	H	S	1	407	2.70
60	16A	F	$PhCH_2$	NH	H	S	1	408	2.60
61	16B	F	$Ph(CH_2)_2$	NH	H	S	1	422	2.68
62	18	B	Ph	bond	Me	S	1	393	2.62
63	18	B	$PhCH_2$	bond	Me	S	1	407	2.64
64	18	B	$Ph(CH_2)_2$	bond	Me	S	1	421	2.70
65	18	C	$PhCH_2$	NH	Me	S	1	422	2.65

Ex.	From Int. No.	Synthetic Method	R	X	R'	Stereochem at position "*"	n	LCMS [M+H]+ observed	HPLC R_t (min)
66	18	C	$Ph(CH_2)_2$	NH	Me	S	1	436	2.71
67	24B	F	$Ph(CH_2)_2$	NH	H	R	1	422	2.62/2.66
68	24A	F	$PhCH_2$	NH	H	R	1	408	2.54/2.59
69	23A	D	Ph	bond	H	R	1	379	2.5/2.55
70	23B	D	$PhCH_2$	bond	H	R	1	393	2.53
71	23C	D	$Ph(CH_2)_2$	bond	H	R	1	407	2.6/2.64
72	26	B	$Ph(CH_2)_2$	bond	Me	R	1	421	2.66
73	26	B	$PhCH_2$	bond	Me	R	1	407	2.6
74	26	B	Ph	bond	Me	R	1	393	2.57

Ex.	From Int. No.	Synthetic Method	R	X	R'	Stereochem at position "*"	n	LCMS [M+H]+ observed	HPLC R_t (min)
75	26	C	$Ph(CH_2)_2$	NH	Me	R	1	436	2.73
76	26	C	$PhCH_2$	NH	Me	R	1	422	2.66
77	23D	D	4-(cPrNHCO) $C_6H_4CH_2$	bond	H	R	1	476	2.46

Table D



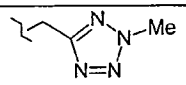
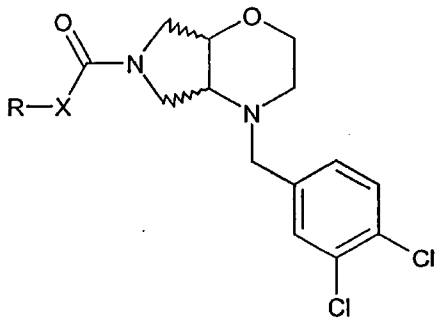
Ex.	From Int. No.	Synthetic Method	R	X	n	LCMS [M+H]+ observed	HPLC R_t (min)
1	5	B	$PhCH_2$	bond	0	409	2.79
2	5	B	Ph	bond	0	395	2.74
3	5	B	$Ph(CH_2)_2$	bond	0	423	2.90
4	5	B	$4\text{-}(cPrNHCO)C_6H_4CH_2$	bond	0	492	2.59
5	5	B	$3\text{-}(cPrNHCO)C_6H_4CH_2$	bond	0	492	2.50
8	5	A	$3\text{-}(CONH_2)C_6H_4CH_2$	NH	0	467	2.34
7	5	A	$Ph(CH_2)_2$	NH	0	438	2.80
6	5	A	$PhCH_2$	NH	0	424	2.72
14	5	C	Ph	NH	0	410	2.84
9	5	A		NH	0	430	2.30
15	8	B	$PhCH_2$	bond	1	425	2.83 + 3.04
13	8	C	$PhCH_2$ isomer1	NH	1	440	2.82
12	8	C	$PhCH_2$ isomer2	NH	1	440	2.99
11	8	C	$PhCH_2$	NH	1	440	2.83 + 2.97
10	10	C	$PhCH_2$	NH	2	456	3.29
16	10	B	$PhCH_2$	bond	2	441	3.30

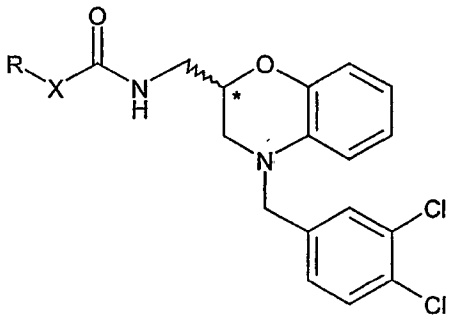
Table E



Ex.	From Int. No.	Synthetic Method	R	X	Stereochem	LCMS [M+H]+ observed	HPLC R_t (min)
78	61	A	Ph	bond	*trans*	391	3.33
79	61	A	$Ph(CH_2)_2$	bond	*trans*	419	3.53
80	61	B	$PhCH_2$	NH	*trans*	420	3.34
81	61	B	$Ph(CH_2)_2$	NH	*trans*	434	3.44
82	61	B	$3\text{-}(MeNHCO)C_6H_4CH_2$	NH	*trans*	477	2.94
83	58	B	$Ph(CH_2)_2$	bond	*cis*	419	3.53
84	58	C	$PhCH_2$	NH	*cis*	420	3.32
85	58	C	$Ph(CH_2)_2$	NH	*cis*	434	3.39
86	58	B	Ph	bond	*cis*	391	3.35
87	58	B	$PhCH_2$	bond	*cis*	405	3.41

5

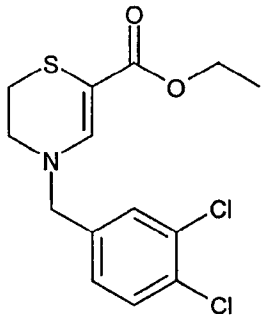
Table F



Ex.	From Int. No.	Synthetic Method	R	X	Stereochem	LCMS [M+H]+ observed	HPLC R_t (min)
46	40	B	$Ph(CH_2)_2$	bond	RS	455	3.9
47	40	B	$PhCH_2$	bond	RS	441	3.84
48	40	B	Ph	bond	RS	427	3.87
49	40	C	$PhCH_2$	NH	RS	456	3.66

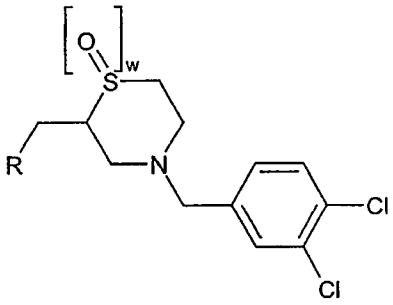
5

Table G



Intermediate 1

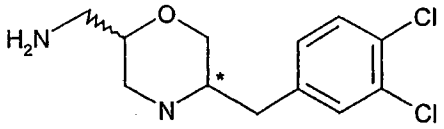
Table H



Intermediate	R	w
2	HO	0
3	Cl	0
4	N_3	0
5	H_2N	0
6	t-BuOC(O)NH	0
7	t-BuOC(O)NH	1
8	H_2N	1
9	t-BuOC(O)NH	2
10*	H_2N	2

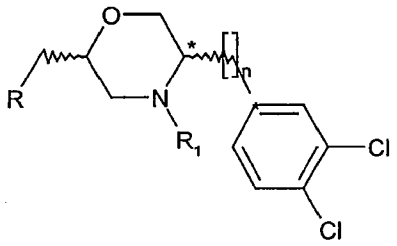
* trifluoroacetate

Table I



Intermediate 11 (Stereochemistry at position "*" = L)
Intermediate 19 (Stereochemistry at position "*" = D)

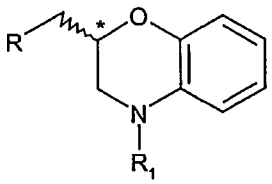
Table J



Intermediate	R	R_1	n	Stereochemistry at position "*"
12	$CF_3C(O)NH$	H	1	S
13	$CF_3C(O)NH$	t-BuOC(O)	1	S
14	H_2N	t-BuOC(O)	1	S
15A	PhC(O)NH	t-BuOC(O)	1	S
15B	BnC(O)NH	t-BuOC(O)	1	S
15C	$BnCH_2C(O)NH$	t-BuOC(O)	1	S
16A	BnNHC(O)NH	t-BuOC(O)	1	S
16B	$BnCH_2NHC(O)NH$	t-BuOC(O)	1	S
17	$CF_3C(O)NH$	Me	1	S
18	H_2N	Me	1	S
20	$CF_3C(O)NH$	H	1	R
21	$CF_3C(O)NH$	t-BuOC(O)	1	R
22	H_2N	t-BuOC(O)	1	R
23A	PhC(O)NH	t-BuOC(O)	1	R
23B	BnC(O)NH	t-BuOC(O)	1	R
23C	$BnCH_2C(O)NH$	t-BuOC(O)	1	R
23D	3-(c-PrNHC(O)Bn)C(O)NH	t-BuOC(O)	1	R

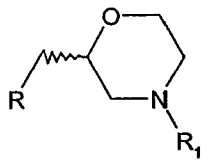
Intermediate	R	R_1	n	Stereochemistry at position "*"
24A	BnNHC(O)NH	t-BuOC(O)	1	R
24B	$BnCH_2NHC(O)NH$	t-BuOC(O)	1	R
25	$CF_3C(O)NH$	Me	1	R
26	H_2N	Me	1	R
27	H_2N	H	0	RS
28	$CF_3C(O)NH$	H	0	R or S
29	$CF_3C(O)NH$	t-BuOC(O)	0	R or S
30	H_2N	t-BuOC(O)	0	R or S
31A	PhC(O)NH	t-BuOC(O)	0	R or S
31B	BnC(O)NH (diastereoisomer 1)	t-BuOC(O)	0	R or S
31C	$BnCH_2C(O)NH$	t-BuOC(O)	0	R or S
32A	BnNHC(O)NH (diastereoisomer 1)	t-BuOC(O)	0	R or S
32B	$BnCH_2NHC(O)NH$	t-BuOC(O)	0	R or S
33	$CF_3C(O)NH$	H	0	R or S
34	$CF_3C(O)NH$	t-BuOC(O)	0	R or S
35	H_2N	t-BuOC(O)	0	R or S
36	BnC(O)NH (diastereoisomer 2)	t-BuOC(O)	0	S or R
37	BnNHC(O)NH (diastereoisomer 2)	t-BuOC(O)	0	S or R

Table K



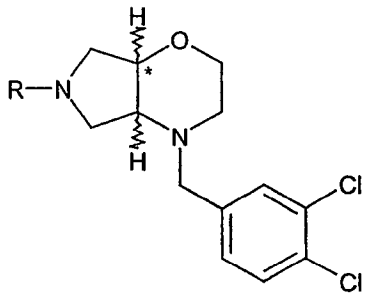
Intermediate	R	R_1	Stereochemistry at position "*"
38	$CF_3C(O)NH$	H	R or S
39	$CF_3C(O)NH$	3,4-di-ClBn	R or S
40	H_2N	3,4-di-ClBn	R or S

Table L



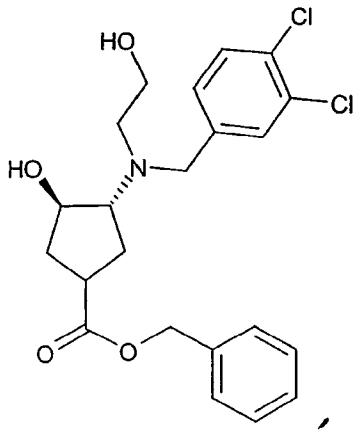
Intermediate	R	R_1
41	$CF_3C(O)NHCH_2$	Bn
42	$CF_3C(O)NHCH_2$	H
43	$CF_3C(O)NHCH_2$	t-BuOC(O)
44	H_2NCH_2	t-BuOC(O)
45	(3,4-di-ClBn)$NHCH_2$	t-BuOC(O)
46	(3,4-di-ClBn)($CF_3C(O)$)NCH_2	t-BuOC(O)
47	(3,4-di-ClBn)($CF_3C(O)$)NCH_2	H
48A	(3,4-di-ClBn)($CF_3C(O)$)NCH_2	Bz
48B	(3,4-di-ClBn)($CF_3C(O)$)NCH_2	BnC(O)
48C	(3,4-di-ClBn)($CF_3C(O)$)NCH_2	$BnCH_2C(O)$
49A	(3,4-di-ClBn)($CF_3C(O)$)NCH_2	BnNHC(O)
49B	(3,4-di-ClBn)($CF_3C(O)$)NCH_2	$BnCH_2NHC(O)$
50	(3,4-di-ClBn)(Me)NCH_2	t-BuOC(O)
51	(3,4-di-ClBn)(Me)NCH_2	H
52	(3,4-di-ClBn)NH	t-BuOC(O)
53	(3,4-di-ClBn)(Me)N	t-BuOC(O)
53A	(3,4-di-ClBn)($CF_3C(O)$)N	t-BuOC(O)
54	(3,4-di-ClBn)(Me)N	H
54A	(3,4-di-ClBn)($CF_3C(O)$)N	H
55A	(3,4-di-ClBn)($CF_3C(O)$)N	Bz
55B	(3,4-di-ClBn)($CF_3C(O)$)N	BnC(O)
55C	(3,4-di-ClBn)($CF_3C(O)$)N	$BnCH_2C(O)$
56A	(3,4-di-ClBn)($CF_3C(O)$)N	BnNHC(O)
56B	(3,4-di-ClBn)($CF_3C(O)$)N	$BnCH_2NHC(O)$

Table M



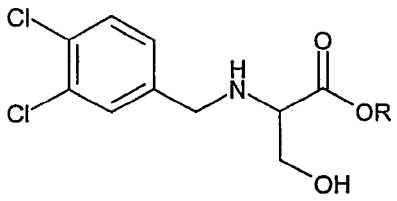
Intermediate (*cis*-fused)	R	Stereochemistry at position "*"
57	t-BuOC(O)	R or S
58	H	R or S
60	BnOC(O)	R or S
61	H	R or S

Table N



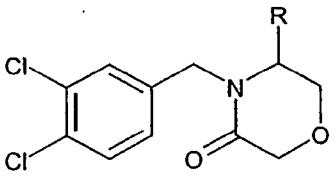
Intermediate 59

Table O



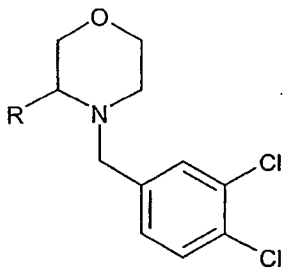
Intermediate 62: R = Me
Intermediate 63: R = H

Table P



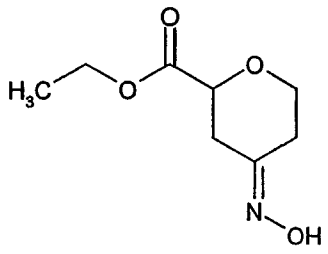
Intermediate	R
64	HOC(O)
65	$H_2NC(O)$
67	$BnOC(O)CH_2$
68	$HOC(O)CH_2$
69	$H_2NC(O)CH_2$

Table Q



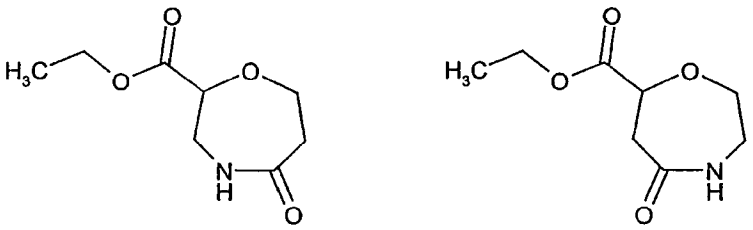
Intermediate 66 (R = $H_2NC(O)$)
Intermediate 70 (R = $H_2N(CH_2)_2$

Table R



Intermediate 76

Table S

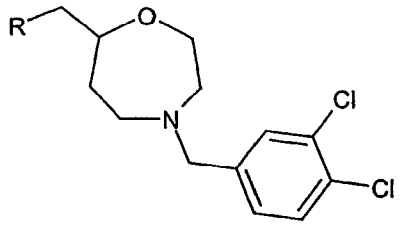


Intermediate 77 (Mixture)

Table T

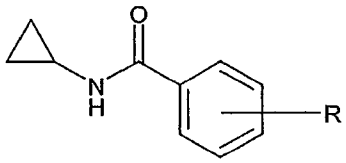
Intermediate 78 (Mixture)

Table U



Intermediate	R
79	HO
80	N_3
81	H_2N

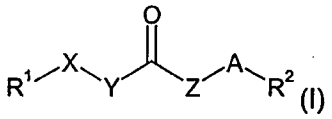
Table V



Intermediate	R
82	3-(MeOC(O)CH_2)-
83	3-(HOC(O)CH_2)-
84	4-(MeOC(O)CH_2)-
85	4-(HOC(O)CH_2)-

Claims

1. A compound of formula (I'):



(I)

wherein:

R^1 represents substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

X represents $-(CR_{ka}R_{kb})_k-$;

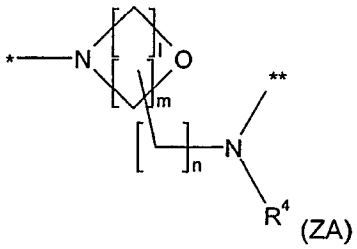
R_{ka} and R_{kb} are each independently hydrogen or C_{1-6}alkyl;

k is 0-5;

Y represents $-NR^3-$ or a bond;

R^3 represents hydrogen or C_{1-6}alkyl;

Z represents a moiety of formula (ZA):



(ZA)

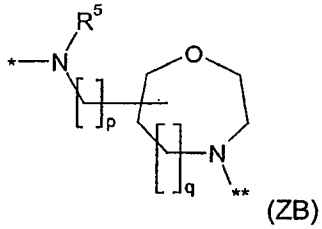
wherein;

l and m are each independently 1 or 2 and l+m is at least 3;

n is 1 or 2, and;

R^4 is hydrogen or C_{1-6}alkyl;

or Z represents a moiety of formula (ZB):



(ZB)

wherein;

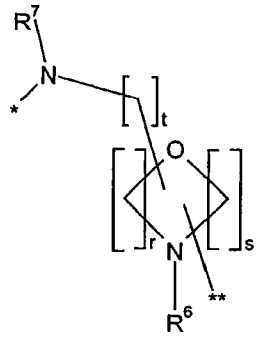
R^5 is hydrogen or C_{1-6}alkyl;

p is 1 or 2, and;

q is 0 or 1;

with the proviso that (ZB) does not represent a 2,4-morphinolyl moiety;

or Z represents a moiety of formula (ZC):



(ZC)

wherein;

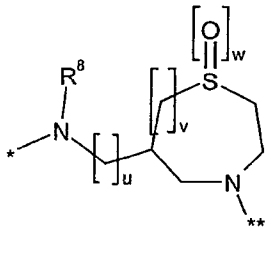
r and s are each independently 1 or 2 and r+s is at least 3;

t is 0, 1, or 2, and;

R^6 is hydrogen or C_{1-6}alkyl;

R^7 is hydrogen or C_{1-6}alkyl;

or Z is a moiety of formula (ZD):



(ZD)

wherein;

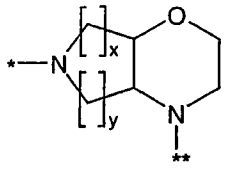
R^8 is hydrogen or C_{1-6}alkyl;

u is 1 or 2;

v is 0 or 1, and;

w is 0, 1, or 2;

or Z is a moiety of formula (ZE)

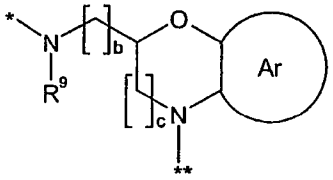


(ZE)

wherein;

x and y are each independently 1 or 2;

or Z represents a moiety of formula (ZF)



(ZF)

wherein;

R^9 is hydrogen or C_{1-6}alkyl;

b is 1 or 2;

c is 1 or 2;

Ar is is a 5 or 6-membered aryl group;

A represents $-(CR_{ja}R_{jb})_j-$;

R_{ja} and R_{jb} are each independently hydrogen or C_{1-6}alkyl;

j is 0, 1 or 2, and;

R^2 represents unsubstituted or substituted aryl;

and salts and solvates thereof, with the proviso that the following compounds are excluded;

4-({[({[4-(3,4-dichlorobenzyl)-1,4-oxazepan-2-yl]methyl}amino)carbonyl]--amino}methyl)benzamide;

2-methoxy-N-[[4-(phenylmethyl)-3-morpholinyl]methyl]benzamide;

N-(3-cyanophenyl)-N'-[[4-(phenylmethyl)-3-morpholinyl]methyl]urea;

cis-6-benzoyloctahydro-4-(phenylmethyl)pyrrolo[3,4-b]-1,4-oxazine;

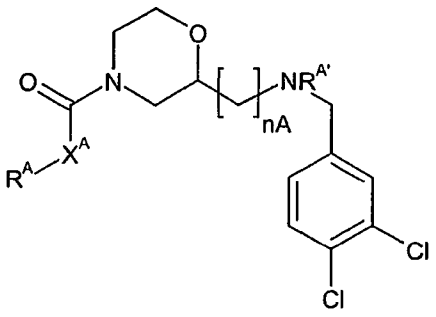
N-[2,6-bis(1-methylethyl)phenyl]-N'-[[6-chloro-3,4-dihydro-4- (phenylmethyl)-2H-1,4-benzoxazin-2-yl]methyl]urea;

N-[2-[2-[3,5-bis(1,1-dimethylethyl)-4-hydroxyphenyl]ethyl]phenyl]-N'- [[4-[(4-fluorophenyl)methyl]-3-morpholinyl]methyl]urea;

cis-6-benzoyloctahydro-4-(phenylmethyl)pyrrolo[3,4-b]-1,4-oxazine;

4-amino-5-chloro-2-ethoxy-N-[[4-(phenylmethyl)-3-morpholinyl]methyl]benzamide, and;
4-amino-5-chloro-2-ethoxy-N-[2-[4-(phenylmethyl)-3-morpholinyl]ethyl]benzamide.

2. A compound according to claim 1 of formula (IA)

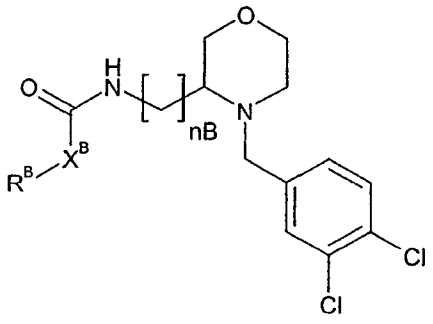


(IA)

wherein;

R^A is unsubstituted aryl or unsubstituted arylC_{1-6}alkyl;
X^A is a bond or -NH-;
nA is 1 or 2;
$R^{A'}$ is C_{1-6}alkyl or hydrogen;
or a salt or solvate thereof.

3. A compound according to claim 1 of formula (IB)



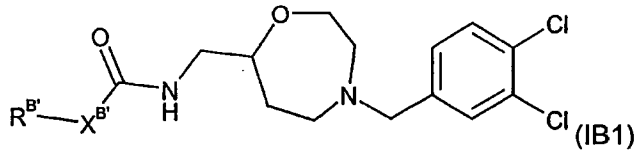
(IB)

wherein;

R^B is unsubstituted aryl or unsubstituted arylC_{1-6}alkyl;
X^B is -NH- or a bond, and;
nB is 1 or 2;

or a salt or solvate thereof.

4. A compound according to claim 1 of formula (IB1)



(IB1)

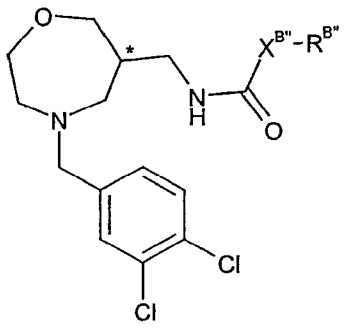
wherein;

$R^{B'}$ is unsubstituted aryl or unsubstituted arylC_{1-6}alkyl, and;

$X^{B'}$ is -NH- or a bond;

or a salt or solvate thereof.

5. A compound according to claim 1 of formula (IB2)



(IB2)

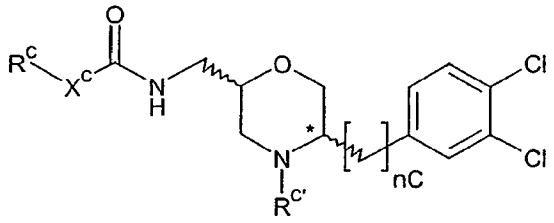
wherein;

$X^{B''}$ is a bond or –NH-, and;

$R^{B''}$ is unsubstituted aryl or unsubstituted arylC_{1-6}alkyl;

or a salt or solvate thereof.

6. A compound according to claim 1 of formula (IC)



(IC)

wherein;

R^C is unsubstituted or aryl or unsubstituted or substituted arylC_{1-6}alkyl;

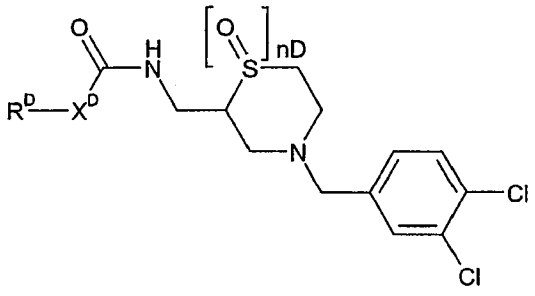
X^C is –NH- or a bond;

$R^{C'}$ is hydrogen or methyl, and;

nC is 0 or 1;

or a salt or solvate thereof.

7. A compound according to claim 1 of formula (ID)



(ID)

wherein;

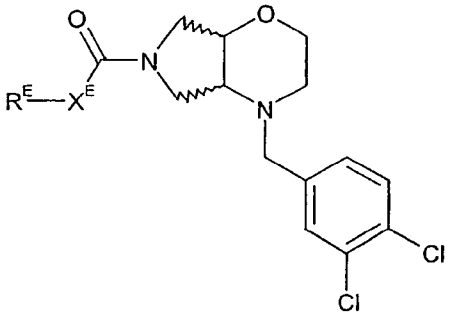
R^D is unsubstituted aryl, unsubstituted or substituted arylC_{1-6}alkyl, or substituted heteroaryl;

X^D is a bond or -NH-, and;

nD is 0, 1, or 2;

or a salt or solvate thereof.

8. A compound according to claim 1 of formula (IE)



(IE)

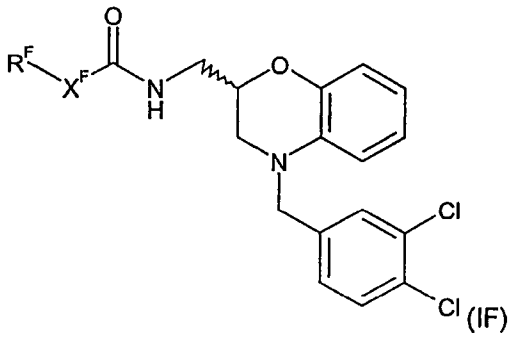
wherein;

R^E is unsubstituted aryl, or unsubstituted or substituted arylC_{1-6}alkyl, and;

X^E is a bond or -NH-;

or a salt or solvate thereof.

9. A compound according to claim 1 of formula (IF)



(IF)

wherein;

R^F is unsubstituted or aryl or unsubstituted arylC_{1-6}alkyl, and;

X^F is a bond or -NH-;

or a salt or solvate thereof.

10. A process for the preparation of a compound of formula (I) as defined in claim 1 wherein Y represents $-NR^3-$ which process comprises two alternatives;

Alternative (i): the reaction of a compound of formula (II), or a protected form thereof, with a compound of formula (III);

$$R^1\text{-}X\text{-}N(R^3)U_g \text{ (II)} \qquad R^2\text{-}A\text{-}ZH \text{ (III)}$$

or;

Alternative (ii): the reaction between a compound of formula (V), or a protected form thereof, with a compound of formula (IV);

$$R^2\text{-}A\text{-}Z\text{-}U_g \text{ (V)} \qquad R^1\text{-}X\text{-}N(R^3)H \text{ (IV)}$$

wherein;

R^1, X, R^3, R^2, A, and Z are as defined in claim 1 and U_g is a urea-forming group,

and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing a salt or solvate of the compound so formed.

11. A process for the preparation of a compound of formula (I) as defined in claim 1 wherein Y represents -NR^3- which process comprises the reaction of a compound of formula (III) as defined in claim 10, or a protected form thereof, with a compound of formula (VI);

R^1-X-NCO (VI)

wherein R^1 and X are as defined in claim 1, and thereafter, if required, carrying out one or more of the following optional steps:

(i) converting a compound of formula (I) into a further compound of formula (I);

(ii) removing any necessary protecting group;

(iii) preparing a salt or solvate of the compound so formed.

12. A process for the preparation of a compound of formula (I) as defined in claim 1 wherein Y is a bond which process comprises the reaction of a compound of formula (VII)

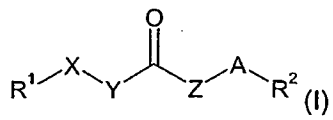
R^1-X-COOH (VII)

wherein R^1 and X are as defined in claim 1, with a compound of formula (III) as defined in claim 10 in the presence of a suitable activating agent.

13. A compound of formula (I') as defined in claim 1, or a physiologically acceptable salt or solvate thereof, for use as an active therapeutic agent.

14. A compound of formula (I') as defined in claim 1, or a physiologically acceptable salt or solvate thereof, for use in the treatment of inflammatory conditions, eg. asthma or rhinitis.

15. Use of a compound of formula (I)



(I)

wherein:

R^1 represents substituted or unsubstituted aryl or substituted or unsubstituted heteroaryl;

X represents $-(CR_{ka}R_{kb})_k-$;

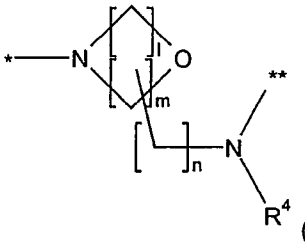
R_{ka} and R_{kb} are each independently hydrogen or C_{1-6}alkyl;

k is 0-5;

Y represents $-NR^3-$ or a bond;

R^3 represents hydrogen or C_{1-6}alkyl;

Z represents a moiety of formula (ZA):



(ZA)

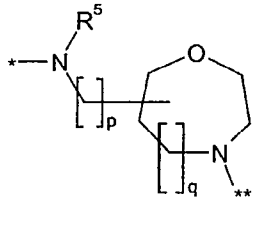
wherein;

l and m are each independently 1 or 2 and l+m is at least 3;

n is 1 or 2, and;

R^4 is hydrogen or C_{1-6}alkyl;

or Z represents a moiety of formula (ZB):



(ZB)

wherein;

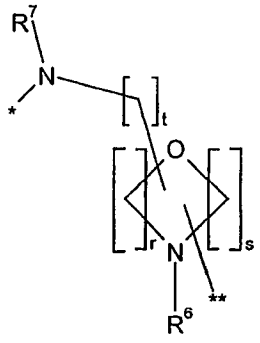
R^5 is hydrogen or C_{1-6}alkyl;

p is 1 or 2, and;

q is 0 or 1;

with the proviso that (ZB) does not represent a 2,4-morphinolyl moiety;

or Z represents a moiety of formula (ZC):



(ZC)

wherein;

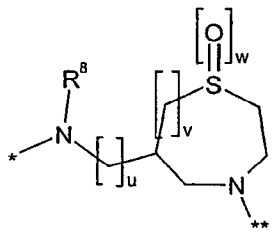
r and s are each independently 1 or 2 and r+s is at least 3;

t is 0, 1, or 2, and;

R^6 is hydrogen or C_{1-6}alkyl;

R^7 is hydrogen or C_{1-6}alkyl;

or Z is a moiety of formula (ZD):



(ZD)

wherein;

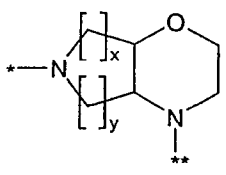
R^8 is hydrogen or C_{1-6}alkyl;

u is 1 or 2;

v is 0 or 1, and;

w is 0, 1, or 2;

or Z is a moiety of formula (ZE)

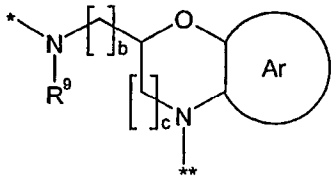


(ZE)

wherein;

x and y are each independently 1 or 2;

or Z represents a moiety of formula (ZF)



(ZF)

wherein;

R^9 is hydrogen or C_{1-6}alkyl;

b is 1 or 2;

c is 1 or 2;

Ar is is a 5 or 6-membered aryl group;

A represents $-(CR_{ja}R_{jb})_j-$;

R_{ja} and R_{jb} are each independently hydrogen or C_{1-6}alkyl;

j is 0, 1 or 2, and;

R^2 represents unsubstituted or substituted aryl;

or a physiologically acceptable salt or solvate thereof, for the manufacture of a medicament for the treatment of patients with inflammatory conditions, eg. asthma or rhinitis, with the proviso that the following compound is excluded; 4-({[({[4-(3,4-dichlorobenzyl)-1,4-oxazepan-2-yl]methyl}amino)carbonyl]--amino}methyl)benzamide.

16. A method for the treatment of a human or animal subject with an inflammatory condition eg. asthma or rhinitis, which method comprises administering an effective amount of a compound of formula (I) as defined in claim 15, or a physiologically acceptable salt or solvate thereof.

17. A pharmaceutical composition comprising a compound of formula (I') as defined in claim 1, or a physiologically acceptable salt or solvate thereof, and optionally one or more physiologically acceptable diluents or carriers.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/05446

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D265/30 C07D267/10 C07D279/12 C07D265/36 C07D417/12
C07D498/04 A61K31/5375 A61K31/54 A61P11/06
//(C07D498/04,265:00,209:00)

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 02 26723 A (HARRISON LEE ANDREW ;JUDD DUNCAN BRUCE (GB); GLAXO GROUP LTD (GB);) 4 April 2002 (2002-04-04) cited in the application claims	1-17
A	WO 02 26722 A (HARRISON LEE ANDREW ;JUDD DUNCAN BRUCE (GB); GLAXO GROUP LTD (GB);) 4 April 2002 (2002-04-04) cited in the application claims	1-17
A	EP 0 760 362 A (NISSHIN FLOUR MILLING CO) 5 March 1997 (1997-03-05) claims	1-17

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
4 September 2003	16/09/2003

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Chouly, J

Form PCT/ISA/210 (second sheet) (July 1992)

INTER[redacted]TIONAL SEARCH REPORT

International [redacted]plication No
PCT/EP 03/05446

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 00 71518 A (SEPRACOR INC) 30 November 2000 (2000-11-30) claims	1-17

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 03/05446

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 16 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 03/05446

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 0226723	A	04-04-2002	AU	9014601 A	08-04-2002
			BR	0114321 A	01-07-2003
			CA	2423305 A1	04-04-2002
			CZ	20031194 A3	13-08-2003
			EP	1324991 A1	09-07-2003
			WO	0226723 A1	04-04-2002
			NO	20031443 A	26-05-2003
WO 0226722	A	04-04-2002	AU	9014301 A	08-04-2002
			BR	0114323 A	01-07-2003
			CA	2423251 A1	04-04-2002
			EP	1324990 A1	09-07-2003
			WO	0226722 A1	04-04-2002
			NO	20031442 A	26-05-2003
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			CA	2189964 A1	23-11-1995
			DE	69527786 D1	19-09-2002
			DE	69527786 T2	10-04-2003
			EP	0760362 A1	05-03-1997
			WO	9531431 A1	23-11-1995
			US	5753654 A	19-05-1998
WO 0071518	A	30-11-2000	AU	5295300 A	12-12-2000
			CA	2372887 A1	30-11-2000
			EP	1187810 A2	20-03-2002
			JP	2003500392 T	07-01-2003
			WO	0071518 A2	30-11-2000
			US	2003069418 A1	10-04-2003